METHODS TO TREAT ALZHEIMER'S DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority of invention under 35 U.S.C. §119(e) from U.S. provisional application number 60/191,528, filed March 23, 2000.

FIELD OF THE INVENTION

The present invention provides compounds, compositions, and methods for inhibiting β-secretase-mediated cleavage of beta amyloid precursor protein. More particularly, the invention relates to the use of the compounds, compositions, and methods of the invention to inhibit the production of beta-beta amyloid peptide and to treat or prevent disease characterized by beta-beta amyloid peptide deposits. Most particularly, the invention provides compounds, compositions, and methods for the treatment of Alzheimer's disease.

BACKGROUND OF THE INVENTION

Alzheimer's Disease (AD) is a degenerative brain disorder presented clinically by progressive loss of memory, cognition, reasoning, judgement, and emotional stability that gradually leads to profound mental deterioration and ultimately death. Individuals with AD exhibit characteristic beta amyloid deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as well as neurofibrillary tangles. On autopsy of AD patients, large numbers of these lesions are generally found in areas of the human brain important for memory and congnitive function. Smaller numbers are found in the brains of most aged humans not showing clinical symptoms of AD. Beta amyloid plaques and beta amyloid angiopathy also characterize the brains of individuals with Down's Syndrome (Trisomy 21) and Hereditary Cerebral Hemorrhage with Beta amyloidosis of the Dutch-Type, and other such disorders.

Beta amyloid plaques are a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Beta amyloid plaques are

predominantly composed of beta amyloid beta peptide (Aβ, also sometimes designated βA4).

Several isotypes of APP are known to date, including "normal" APP-695, APP-751, and APP770, having a sequence of 695, 751, and 770 amino acids, respectively. The identification of mutations in the beta amyloid precursor protein gene that cause familial, early onset AD implicate beta amyloid metabolism in the pathology of the disease. Such reported mutations include the double Swedish mutation (SW), changing Lys^{595} and Met^{596} to Asp^{595}-Leu^{596}, and mutations altering Val^{717} to Gly, Ile, or Phe.

Aβ peptide is derived by proteolysis of the beta amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP. Deposition of Aβ in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Cleavage of APP at the N-terminus of the βA4 peptide by β-secretase and at the C-terminus by one or more γ-secretases constitutes the beta amyloidogenic pathway, i.e. the pathway by which Aβ is formed. Cleavage of APP by α-secretase and the same or a different γ-secretase produces α-sAPP, a secreted form of APP that does not result in beta amyloid plaque formation. This alternate α-sAPP pathway precludes the formation of Aβ peptide. It has been proposed that Aβ accumulates as a result of processing of APP by β-secretase, and that therefore inhibition of the activity of this enzyme is desireable for the treatment of AD. *In vivo* processing of APP at the β-secretase site is thought to be the rate-limiting step in Aβ production, and is thus a therapeutic target for the treatment of AD. See, for example, Sabbagh et. al., 1997, *Alz.Dis.Rev.* 3:1-19). A description of the proteolytic processing fragments of APP can be found, for example, in U.S. Patent Nos. 5,441,870, 5,721,130, and 5,942,400.

Several lines of evidence indicate that progressive cerebral deposition of particular beta amyloidogenic peptides, β-amyloid peptides, (Aβ), play a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Recently, it has been shown that Aβ is released from neuronal cells grown in culture and is present in cerebrospinal fluid (CSF)

of both normal individuals and AD patients. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the β-secretase cleavage site. The β-secretase enzyme has been disclosed using varied nomenclature, including BACE and Asp. See, for example, Sindha et.al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369 (hAsp2a and hAsp2b).

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of β-secretase, that inhibit β-secretase-mediated cleavage of APP, that are effective inhibitors of Aβ production, and/or are effective to reduce beta amyloid beta deposits or plaques are needed for the treatment and prevention of disease characterized by beta amyloid beta deposits or plaques, such as AD.

SUMMARY OF INVENTION

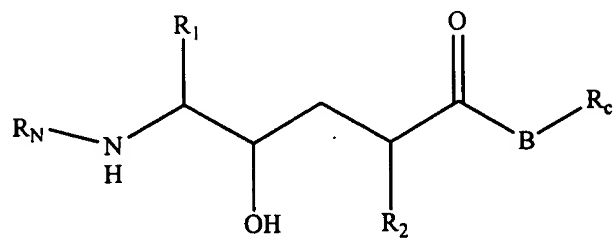
The present invention provides compounds, compositions, and methods for inhibiting β-secretase-mediated cleavage of beta amyloid precursor protein. More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of beta-beta amyloid peptide and to treat or prevent disease characterized by beta-beta amyloid peptide deposits.

Most particularly, the compounds, compositions, and methods of the invention are effective for treating humans who have Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Beta amyloidosis of the Dutch-Type, for treating cerebral beta amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including

dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewis body type of Alzheimer's disease.

The inhibitory activities of the compounds of the invention can be demonstrated, for example, using one or more of the assays described herein or in the prior art.

The compounds (XII) of the invention possess β-secretase inhibitory activity:



(XII)

where R_1 is:

(I) C_1-C_6 alkyl,

(II) C_1-C_6 alkyl-S-alkyl

(III) C_1-C_6 alkyl-(C_2-C_6 alkenyl),

(IV) -$(CH_2)_{0-6}$-alkyl -($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is unsubstituted or substituted with:

(A) C_1-C_6 alkyl,

(B) –CF_3,

(C) -F, Cl, -Br or –I,

(D) C_1-C_3 alkoxy,

(E) –O-CF_3,

(F) -NH_2,

(G) -OH, or

(H) -C≡N,

(V) -$(CH_2)_{0-6}$-alkyl -($R_{1\text{-heteroaryl}}$) where $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{1\text{-heteroaryl}}$ group is bonded to -alkyl- by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where $R_{1\text{-heteroaryl}}$ is unsubstituted or substituted with:

(1) C_1-C_3 alkyl,

(2) $-CF_3$,

(3) -F, Cl, -Br, or I,

(4) C_1-C_3 alkoxy,

(5) $-O-CF_3$,

(6) $-NH_2$,

(7) -OH, or

(8) $-C\equiv N$,

(VI) -($R_{1\text{-heteroaryl}}$) where $R_{1\text{-heteroaryl}}$ is as defined above,

(VII) - C_1-C_5 alkyl-($R_{1\text{-heterocycle}}$) where $R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl,

where the $R_{1\text{-heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{-heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where $R_{1\text{-heterocycle}}$ is unsubstituted or substituted with:

(1) =O,

(2) C_1-C_3 alkyl,

(3) $-CF_3$,

(4) -F, Cl, -Br or –I,

(5) C_1-C_3 alkoxy,

(6) $-O-CF_3$,

(7) $-NH_2$,

(8) -OH, or

(9) -C≡N, or

(VIII) - $R_{1\text{-heterocycle}}$ with $R_{1\text{-heterocycle}}$ as defined above;

where R_2 is:

(I) -H,

(II) alkyl, or

(III) $-C_1$-C_5 alkyl-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is cycloalkyl, $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$ where $R_{1\text{-aryl}}$ and $R_{1\text{-heteroaryl}}$ are as defined above,

where R_N is:

(I) R_{N-1}-X_N- where X_N is:

(A) –CO-,

(B) –SO_2-,

(C) -$(CR'R'')_{1-6}$ where R' and R'' are the same or different and are –H or C_1-C_4 alkyl,

(D) –CO-$(CR'R'')_{1-6}$-X_{N-1} where X_{N-1} is –O-, -S- or –NR'R''- and where R' and R'' are as defined above, or

(E) a single bond;

where R_{N-1} is:

(A) $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is unsubstituted or substituted with:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) -NO_2,

(5) -CO-OH,

(6) -C≡N,

(7) -CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) -C_1-C_6 alkyl unsubstituted or substituted with

(i) -OH, or

(ii) -NH_2,

(c) -C_1-C_6 alkyl unsubstituted or substituted with –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_1-C_6 alkenyl with one or two double bonds,

(h) -C_1-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) -$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with C_1-C_3 alkyl,

(13) -CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is:

(a) alkyl, or

(b) -$(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(21) -$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ can be the same or different and are as defined above,

(22) -$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH,

(28) -S-(C_1-C_6 alkyl),

(29) C_1-C_6 alkyl unsubstituted or substituted with halo,

(30) –O-(C_1-C_6 alkyl unsubstituted or substituted with halo), or

(31) –O-φ,

(B) -$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or-

(YY) pyridopyridinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where $_{N\text{-heteroaryl}}$ is unsubstituted or substituted with:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1-C_6$ alkyl unsubstituted or substituted with:

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1-C_6$ alkyl substituted or substituted with –F, -Cl, -Br, or -I,

(d) $-C_3-C_7$ cycloalkyl,

(e $-(C_1-C_2$ alkyl)-(C_3-C_7 cycloalkyl),

(f) $-(C_1-C_6$ alkyl)-O-(C_1-C_3 alkyl),

(g) $-C_1-C_6$ alkenyl with one or two double bonds,

(h) $-C_1-C_6$ alkynyl with one or two triple bonds,

(i) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) $-CO-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) $-CO-R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-R_{N-4} where R_{N-4} is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with C_1-C_3 alkyl,

(13) -CO-O-R_{N-5} where R_{N-5} is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-R_{N-5} where R_{N-5} is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-R_{N-5} where R_{N-5} is as defined above,

(21) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) -R_{N-4} where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH, or

(28) -S-(C_1-C_6 alkyl),

(C) -$R_{N\text{-aryl}}$-$R_{N\text{-aryl}}$ where -$R_{N\text{-aryl}}$ is as defined above,

(D) -$R_{N\text{-aryl}}$-$R_{N\text{-heteroaryl}}$ where -$R_{N\text{-aryl}}$ and -$R_{N\text{-heteroaryl}}$ are as defined above,

(E) $-R_{N\text{-heteroaryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(F) $-R_{N\text{-heteroaryl}}-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(G) $-R_{N\text{-aryl}}-O-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(H) $-R_{N\text{-aryl}}-S-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(I) $-R_{N\text{-heteroaryl}}-O-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(J) $-R_{N\text{-heteroaryl}}-S-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(K) $-R_{N\text{-aryl}}-CO-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(L) $-R_{N\text{-aryl}}-CO-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above,

(M) $-R_{N\text{-aryl}}-SO_2-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(N) $-R_{N\text{-heteroaryl}}-CO-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(O) $-R_{N\text{-heteroaryl}}-SO_2-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(P) $-R_{N\text{-aryl}}-O-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(Q) $-R_{N\text{-aryl}}-S-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(R) $-R_{N\text{-heteroaryl}}-O-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above, or

(S) $-R_{N\text{-heteroaryl}}-S-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(II) $-CO-(C_1-C_6$ alkyl) where alkyl is unsubstituted or substituted with:

(A) -OH,

(B) $-C_1-C_6$ alkoxy,

(C) $-C_1-C_6$ thioalkoxy,

(D) $-CO-O-R_{N-8}$ where R_{N-8} is $-H$, C_1-C_6 alkyl or $-\phi$,

(E) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) $-CO-R_{N-4}$ where R_{N-4} is as defined above,

(G) $-SO_2-(C_1-C_8$ alkyl),

(H) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) $-O-CO-NR_{N-8}R_{N-8}$ where the RN-8are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(III) –CO-(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with:

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) $–CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) $-O-CO-NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(IV) –CO-(C_1-C_3 alkyl)-S-(C_1-C_3 alkyl) where alkyl is:

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -φ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(V) –CO-CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$-R_{N-aryl}/$R_{N-heteroaryl}$) where R_{N-aryl} and $R_{N-heteroaryl}$ are as defined above, where R_{N-10} is selected from the group consisting of:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) R_{1-aryl} where R_{1-aryl} is as defined above, or

(G) $R_{N-heteroaryl}$ where $R_{N-heteroaryl}$ is as defined above;

where B is -O-, -NH-, or -N(C_1-C_6 alkyl)-;

where R_C is:

(I) C_1-C_8 alkyl unsubstituted or substituted with –OH, –O-ϕ, halo, or (C_1-C_6 alkoxy unsubstituted or substituted with halo),

(II) -$(CH_2)_{0-3}$-alkyl -(C_3-C_7) cycloalkyl where cycloalkyl is unsubstituted or substituted with:

(A) C_1-C_3 alkyl unsubstituted or substituted with–F, -Cl, -Br, or -I,

(B) -CO-OH,

(C) -CO-O-(C_1-C_4 alkyl),

(D) -OH, or

(E) C_1-C_6 alkoxy,

(III) -$(CH_2)_{2-6}$-OH,

(IV) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are –H, C_1-C_4 alkyl and ϕ- and R_{C-aryl} is the same as R_{N-aryl},

(V) -$(CH_2)_{0-4}$-$R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is the same as $R_{N-heteroaryl}$,

(VI) -$(CH_2)_{0-4}$-$R_{C-heterocycle}$ where $R_{C-heterocycle}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) isoxazolyl,

(Q) pyrazolyl,

(R) indolizinyl,

(S) indazolyl,

(T) benzothiazolyl,

(U) benzimidazolyl,

(V) benzofuranyl,

(W) furanyl,

(X) thienyl,

(Y) pyrrolyl,

(Z) oxadiazolyl,

(AA) thiadiazolyl,

(BB) triazolyl,

(CC) tetrazolyl,

(DD) 1, 4-benzodioxan

(EE) purinyl,

(FF) oxazolopyridinyl,

(GG) imidazopyridinyl,

(HH) isothiazolyl,

(II) naphthyridinyl,

(JJ) cinnolinyl,

(KK) carbazolyl,

(LL) β-carbolinyl,

(MM) isochromanyl,

(NN) chromanyl,

(OO) furazanyl,

(PP) tetrahydroisoquinoline,

(QQ) isoindolinyl,

(RR) isobenzotetrahydrofuranyl,

(SS) isobenzotetrahydrothienyl,

(TT) isobenzothiophenyl,

(UU) benzoxazolyl, or

(VV) pyridopyridinyl,

(VII) $-C(R_{C-1})(R_{C-2})-CO-NH-R_{C-3}$ where R_{C-1} and R_{C-2} are the same or different and are:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-(C_1-C_4$ alkyl$)-R_{C'-aryl}$ where $R_{C'-aryl}$ is as defined for R_{1-aryl},

(D) $-(C_1-C_4$ alkyl$)-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is as defined above,

(E) $-(C_1-C_4$ alkyl$)-R_{C-heterocycle}$ where $R_{C-heterocycle}$ is as defined above,

(F) $-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is as defined above,

(G) $-R_{C-heterocycle}$ where $R_{C-heterocycle}$ is as defined above,

(H) $-(CH_2)_{1-4}-OH$,

(I) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C'-aryl}$ where R_{C-4} is $-O-$, $-S-$, $-NH-$, or $-NR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl, and where $R_{C'-aryl}$ is defined above,

(J) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C-heteroaryl}$ where R_{C-4} and $R_{C-heteroaryl}$ are as defined above, or

(K) $-R_{C'-aryl}$ where $R_{C'-aryl}$ is as defined above,

and where R_{C-3} is:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-R_{C'-aryl}$ where $R_{C'-aryl}$ is as defined above,

(D) $-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is as defined above,

(E) $-R_{C-heterocycle}$ where $R_{C-heterocycle}$ is as defined above,

(F) $-(C_1-C_4$ alkyl$)-R_{C'-aryl}$ where $R_{C'-aryl}$ is as defined above,

(G) $-(C_1-C_4$ alkyl$)-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is as defined above, or

(H) $-(C_1-C_4$ alkyl$)-R_{C-heterocycle}$ where $R_{C-heterocycle}$ is as defined above,

(VIII) -CH(ϕ)$_2$,

(IX) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with:

(A) C_1-C_3 alkyl,

(B) –CF_3,

(C) -F, Cl, -Br or –I,

(D) C_1-C_3 alkoxy,

(E) -OCF_3,

(F) -NH_2,

(G) -OH, or

(H) -C≡N,

(X) –CH_2-C≡CH;

(XI) –$(CH_2)_{0-1}$-CHR_{C-5}-$(CH_2)_{0-1}$-ϕ where R_{C-5} is:

(A) –OH, or

(B)-CH_2-OH;

(XII) –CH(-ϕ)-CO-O(C_1-C_3 alkyl);

(XIII) –CH(-CH_2-OH)-CH(-OH)-ϕ-NO_2;

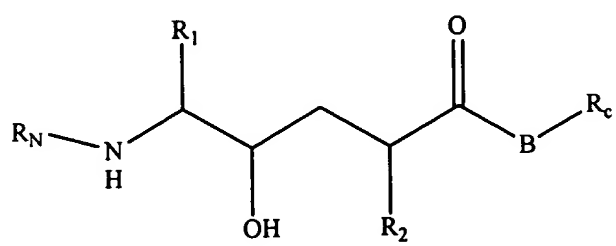
(XIV) –$(CH_2)_2$-O-$(CH_2)_2$-OH;

(XV) –CH_2-NH-CH_2-CH(-O-CH_2-CH_3)$_2$;

(XVI) -(C_2-C_8) alkynyl; or

(XVII) –H; and pharmaceutically acceptable salts thereof.

Also disclosed are hydroxyethylene compounds of the formula (XII)



(XII)

where R_1 is:

(I) C_1-C_6 alkyl, unsubstituted or substituted with one, two or three C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, $-NH_2$, -C≡N, $-CF_3$, or $-N_3$,

(II) $-(CH_2)_{1-2}$-S-CH_3,

(III) $-CH_2$-CH_2-S-CH_3,

(IV) $-CH_2$-(C_2-C_6 alkenyl) unsubstituted or substituted by one –F,

(V) $-(CH_2)_{0-3}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-O-CF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) -C≡N,

(VI) $-(CH_2)_{n1}$-($R_{1\text{-heteroaryl}}$) where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{0\text{-}3}$- by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_3 alkyl,

(2) $-CF_3$,

(3) -F, Cl, -Br, or –I,

(4) C_1-C_3 alkoxy,

(5) $-O-CF_3$,

(6) $-NH_2$,

(7) -OH, or

(8) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VII) $-(CH_2)_{n1}-(R_{1\text{-heterocycle}})$ where n_1 is as defined above and

$R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl,

where the $R_{1\text{-heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{-heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or two:

(1) =O,

(2) C_1-C_3 alkyl,

(3) –CF_3,

(4) -F, Cl, -Br and –I,

(5) C_1-C_3 alkoxy,

(6) –O-CF_3,

(7) -NH_2,

(8) -OH, or

(9) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;

where R_2 is:

(I) -H,

(II) C_1-C_6 alkyl, or

(III) -$(CH_2)_{0\text{-}4}$-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is (C_3-C_6)cycloalkyl, $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$ where $R_{1\text{-aryl}}$ and $R_{1\text{-heteroaryl}}$ are as defined above,

where R_N is:

(I) $R_{N\text{-}1}$-X_N- where X_N is:

(A) –CO-,

(B) –SO_2-,

(C) -$(CR'R'')_{1\text{-}6}$ where R' and R'' are the same or different and are –H or C_1-C_4 alkyl,

(D) $-CO-(CR'R'')_{1-6}-X_{N-1}$ where X_{N-1} is –O-, -S- and –NR'R"- and where R' and R" are as defined above,

(E) a single bond;

where R_{N-1} is:

(A) R_{N-aryl} where R_{N-aryl} is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with one, two, three or four of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) -C_1-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) -C_1-C_6 alkyl unsubstituted or substituted with one to three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_1-C_6 alkenyl with one or two double bonds,

(h) -C_1-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) $-R_{1-aryl}$ where R_{1-aryl} is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(21) -$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ can be the same or different and are as defined above,

(22) -$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH,

(28) -S-(C_1-C_6 alkyl),

(29) C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F,

(30) –O-(C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F, or

(31) –O-ϕ,

(B) -$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or - I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1-C_6$ alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1-C_6$ alkyl unsubstituted or substituted with 1, 2, or 3 –F, -Cl, -Br, or -I,

(d) $-C_3-C_7$ cycloalkyl,

(e $-(C_1-C_2$ alkyl)-$(C_3-C_7$ cycloalkyl),

(f) $-(C_1-C_6$ alkyl)-O-$(C_1-C_3$ älkyl),

(g) $-C_1-C_6$ alkenyl with one or two double bonds,

(h) $-C_1-C_6$ alkynyl with one or two triple bonds,

(i) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-$(C_3-C_{12}$ alkyl),

(9) -CO-$(C_3-C_6$ cycloalkyl),

(10) $-CO-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-R_{N-4} where R_{N-4} is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-R_{N-5} where R_{N-5} is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-R_{N-5} where R_{N-5} is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl$)_2$,

(19) -N-CS-N(C_1-C_3 alkyl$)_2$,

(20) –N(C_1-C_3 alkyl)-CO-R_{N-5} where R_{N-5} is as defined above,

(21) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) -R_{N-4} where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl$)_2$,

(25) -O-CS-N(C_1-C_3 alkyl$)_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH, or

(28) -S-(C_1-C_6 alkyl),

(C) -$R_{N\text{-aryl}}$-$R_{N\text{-aryl}}$ where -$R_{N\text{-aryl}}$ is as defined above,

(D) $-R_{N\text{-aryl}}-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(E) $-R_{N\text{-heteroaryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(F) $-R_{N\text{-heteroaryl}}-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(G) $-R_{N\text{-aryl}}-O-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(H) $-R_{N\text{-aryl}}-S-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(I) $-R_{N\text{-heteroaryl}}-O-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(J) $-R_{N\text{-heteroaryl}}-S-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(K) $-R_{N\text{-aryl}}-CO-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(L) $-R_{N\text{-aryl}}-CO-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above,

(M) $-R_{N\text{-aryl}}-SO_2-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(N) $-R_{N\text{-heteroaryl}}-CO-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(O) $-R_{N\text{-heteroaryl}}-SO_2-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(P) $-R_{N\text{-aryl}}-O-(C_1-C_8\text{ alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(Q) $-R_{N\text{-aryl}}-S-(C_1-C_8\text{ alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(R) $-R_{N\text{-heteroaryl}}-O-(C_1-C_8\text{ alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above, or

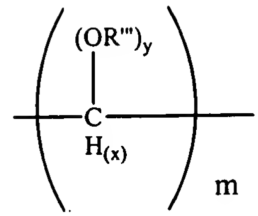
(S) $-R_{N\text{-heteroaryl}}-S-(C_1-C_8\text{ alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(II) $A-X_N-$ where X_N is –CO-,

wherein A is

(A) $-T-E-(Q)_{m'}$,

(1) where $-T$ is



where

(a) $x = 1$ when $y = 1$ and $x = 2$ when $y = 0$,

(b) m is 0, 1, 2 or 3,

(c) the values of x and y vary independently on each carbon when m is 2 and 3, and

(d) R''' varies independently on each carbon and is H, $(C_1\text{-}C_2)$ alkyl, phenyl, or phenyl$(C_1\text{-}C_3)$alkyl;

(2) -E is

(a) $C_1\text{-}C_5$ alkyl, but only if m' does not equal 0,

(b) methylthioxy$(C_2\text{-}C_4)$alkyl,

(c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,

(f) biphenyl,

(g) diphenyl ether,

(h) diphenylketone,

(i) phenyl$(C_1\text{-}C_8)$alkyloxyphenyl, or

(j) $C_1\text{-}C_6$ alkoxy;

(3) -Q is

(a) $C_1\text{-}C_3$ alkyl,

(b) $C_1\text{-}C_3$ alkoxy,

(c) $C_1\text{-}C_3$ alkylthioxy,

(d) C_1-C_6 alkylacylamino,

(e) C_1-C_6 alkylacyloxy,

(f) amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary amino moieties),

(g) C_1-C_6 alkylamino

(h) phenylamino,

(i) carbamyl (including C_1-C_6 alkyl and phenyl amides and esters),

(j) carboxyl (including C_1-C_6 alkyl and phenyl esters),

(k) carboxy(C_2-C_5)alkoxy,

(l) carboxy(C_2-C5)alkylthioxy,

(m) heterocyclylacyl,

(n) heteroarylacyl, or

(o) hydroxyl;

(4) m' is 0, 1, 2 or 3;

(B) -E(Q)$_{m''}$ wherein E and -Q are as defined as above and m" is 0, 1, 2, or 3;

(C) -T-E wherein -E and -Q are as defined as above; or

(D) -E wherein -E is as defined as above;

(III) –CO-(C_1-C_6 alkyl) where alkyl is unsubstituted or substituted with one or two:

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-N$R_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} is the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(IV) –CO-(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(V) –CO-(C_1-C_3 alkyl)-S-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(VI) –CO-CH(-(CH_2)$_{0-2}$-O-R_{N-10})-(CH_2)$_{0-2}$-R_{N-aryl}/$R_{N-heteroaryl}$) where R_{N-aryl} and $R_{N-heteroaryl}$ are as defined above, where R_{N-10} is:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) $R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(G) $R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above;

where B is -O-, -NH-, or -N(C_1-C_6 alkyl)-;

where R_C is:

(I) -(C_1-C_{10})alkyl-$K_{1\text{-}3}$ in which:

(A) the alkyl chain is unsubstituted or substituted with one –OH,

(B) the alkyl chain is unsubstituted or substituted with one C_1-C_6 alkoxy unsubstituted or substituted with 1-5 -F,

(C) the alkyl chain is unsubstituted or substituted with one –O-ϕ,

(D) the alkyl chain is unsubstituted or substituted with 1-5 –F,

(E) the alkyl chain is unsubstituted or substituted with a combination of up to three atoms of oxygen and sulfur each such atom replacing one carbon,

(F) each K is:

(1) H,

(2) C_1-C_3 alkyl,

(3) C_1-C_3 alkoxy,

(4) C_1-C_3 alkylthioxy,

(5) C_1-C_6 alkylacylamino,

(6) C_1-C_6 alkylacyloxy,

(7) amido

(8) C_1-C_6 alkylamino

(9) phenylamino,

(10) carbamyl

(11) carboxyl

(12) carboxy(C_2-C_5)alkoxy,

(13) carboxy(C_2-C5)alkylthioxy,

(14) heterocyclylacyl,

(15) heteroarylacyl,

(16) amino unsubstituted or substituted with C_1-C_6 alkyl,

(17) hydroxyl, or

(18) carboxyl methyl ester;

(II)-$(CH_2)_{0-3}$-J-[(-$(CH_2)_{0-3}$-K]$_{1-3}$ where K is as defined above and J is:

(A) a 5 to 7 atom monocyclic aryl group,

(B) a 8 to 12 atom multicyclic aryl group,

(C) a 5 to 7 atom heterocyclic group,

(D) a 8 to 12 atom multicyclic heterocyclic group, or

(E) a 5 to 10 atom monocyclic or multicyclic cycloalkyl group;

(III) -$(CH_2)_{0-3}$-(C_3-C_7) cycloalkyl where cycloalkyl can be unsubstituted or substituted with one, two or three

(A) C_1-C_3 alkyl unsubstituted or substituted with 1, 2, 3, or 4 –F, -Cl, -Br, or -I,

(B) -CO-OH,

(C) -CO-O-(C_1-C_4 alkyl),

(D) -OH, or

(E) C_1-C_6 alkoxy,

(IV) -$(CH_2)_{2-6}$-OH,

(V) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are –H, C_1-C_4 alkyl and ϕ- and R_{C-aryl} is the same as R_{N-aryl},

(VI) -$(CH_2)_{0-4}$-$R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) isoxazolyl,

(Q) pyrazolyl,

(R) indolizinyl,

(S) indazolyl,

(T) benzothiazolyl,

(U) benzimidazolyl,

(V) benzofuranyl,

(W) furanyl,

(X) thienyl,

(Y) pyrrolyl,

(Z) oxadiazolyl,

(AA) thiadiazolyl,

(BB) triazolyl,

(CC) tetrazolyl,

(DD) 1, 4-benzodioxan

(EE) purinyl,

(FF) oxazolopyridinyl,

(GG) imidazopyridinyl,

(HH) isothiazolyl,

(II) naphthyridinyl,

(JJ) cinnolinyl,

(KK) carbazolyl,

(LL) β-carbolinyl,

(MM) isochromanyl,

(NN) chromanyl,

(OO) furazanyl,

(PP) tetrahydroisoquinoline,

(QQ) isoindolinyl,

(RR) isobenzotetrahydrofuranyl,

(SS) isobenzotetrahydrothienyl,

(TT) isobenzothiophenyl,

(UU) benzoxazolyl, or

(VV) pyridopyridinyl,

(VII) $-(CH_2)_{0-4}-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is the same as $R_{1\text{-heterocycle}}$,

(VIII) $-C(R_{C-1})(R_{C-2})-CO-NH-R_{C-3}$ where R_{C-1} and R_{C-2} are the same or different and are:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-(C_1-C_4$ alkyl$)-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above for $R_{1\text{-aryl}}$,

(D) $-(C_1-C_4$ alkyl$)-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) $-(C_1-C_4$ alkyl$)-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(G) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(H) $-(CH_2)_{1-4}-OH$,

(I) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C'\text{-aryl}}$ where R_{C-4} is –O-, -S-, -NH- or $-NHR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl, and where $R_{C'\text{-aryl}}$ is as defined above,

(J) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C\text{-heteroaryl}}$ where R_{C-4} and $R_{C\text{-heteroaryl}}$ are as defined above, or

(K) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

and where R_{C-3} is:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(D) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) -(C_1-C_4 alkyl)-$R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(G) -(C_1-C_4 alkyl)-$R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above, or

(H) -(C_1-C_4 alkyl)-$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(IX) -CH(ϕ)$_2$,

(X) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one, two or three:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-OCF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) -C≡N,

(XI) $-CH_2$-C≡CH;

(XII) $-(CH_2)_{0\text{-}1}$-$CHR_{C\text{-}5}$-$(CH_2)_{0\text{-}1}$-ϕ where $R_{C\text{-}5}$ is:

(A) –OH, or

(B)-CH_2-OH;

(XIII) –CH(-ϕ)-CO-O(C_1-C_3 alkyl);

(XIV) –CH(-CH_2-OH)-CH(-OH)-ϕ-NO_2;

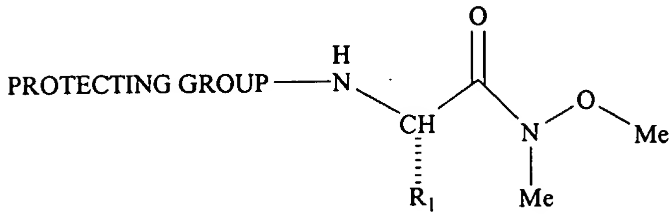
(XV) $-(CH_2)_2$-O-$(CH_2)_2$-OH;

(XVI) $-CH_2$-NH-CH_2-CH(-O-CH_2-CH_3)$_2$;

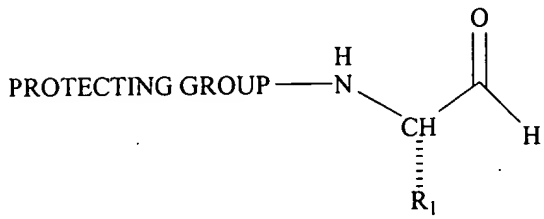
(XVII) -(C_2-C_8) alkynyl; or

(XVIII) –H; or a pharmaceutically acceptable salt thereof.

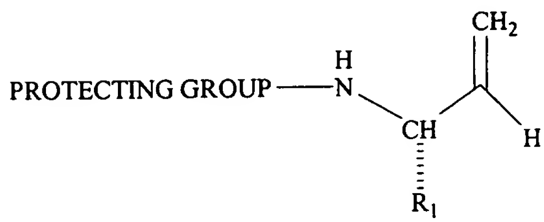
Additionally disclosed are compounds of the formula



(III),



(IV), and



(V),

where R_1 is:

(V) $-CH_2$-phenyl, where phenyl is substituted with two -F in the 3- and 5-positions giving 3, 5-difluorophenyl, or

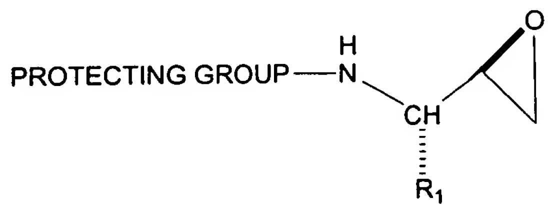
(VI) $-(CH_2)_{n1}-(R_{1\text{-heteroaryl}})$, where n1 and $R_{1\text{-heteroaryl}}$ are as defined above;

and

PROTECTING GROUP is *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-

(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxazoylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl, -phenyl-C(=N)-H, or 1-piperidyloxycarbonyl.

Additionally disclosed are epoxide compounds of the formula



(VI),

where R_1 is:

(A) $-CH_2-\phi$ where $-\phi$ is substituted with two $-F$,

(B) $-(CH_2)_{n1}-R_{1\text{-heteroaryl}}$ where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,
(R) pyrazolyl,
(S) oxazolyl,
(T) thiazolyl,
(U) indolizinyl,
(V) indazolyl,
(W) benzothiazolyl,
(X) benzimidazolyl,
(Y) benzofuranyl,
(Z) furanyl,
(AA) thienyl,
(BB) pyrrolyl,
(CC) oxadiazolyl,
(DD) thiadiazolyl,
(EE) triazolyl,
(FF) tetrazolyl,
(GG) 1, 4-benzodioxan
(HH) purinyl,
(II) oxazolopyridinyl,
(JJ) imidazopyridinyl,
(KK) isothiazolyl,
(LL) naphthyridinyl,
(MM) cinnolinyl,
(NN) carbazolyl,
(OO) β-carbolinyl,
(PP) isochromanyl,
(QQ) chromanyl,
(RR) furazanyl,
(SS) tetrahydroisoquinoline,
(TT) isoindolinyl,
(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

(C) $-(CH_2)_{n1}-R_{1\text{-heterocycle}}$ where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

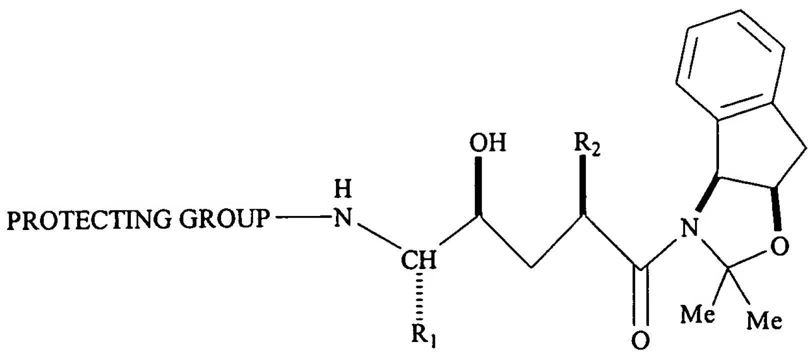
(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl, and

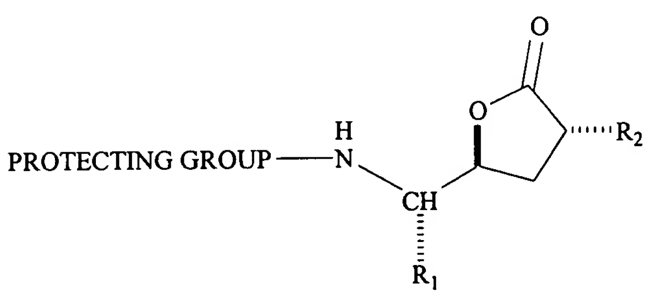
PROTECTING GROUP is *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxazoylmethoxycarbonyl, 4-

acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl, -phenyl-C(=N)-H, or 1-piperidyloxycarbonyl.

Additionally disclosed are compounds of the formula



(VIII), and



(IX)

where R_1 is:

(V) -CH_2-phenyl, where phenyl is substituted with two -F in the 3- and 5-positions giving 3, 5-difluorophenyl, or

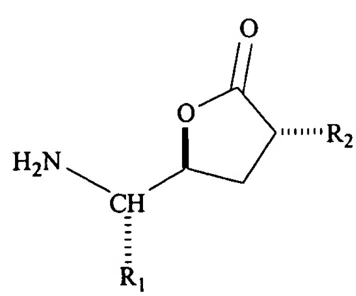
(VI) -$(CH_2)_{n1}$-($R_{1\text{-heteroaryl}}$), where n1 and $R_{1\text{-heteroaryl}}$ are as defined above;

where R_2 is as defined in claim 1; and

PROTECTING GROUP is *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-

yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxazoylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl, -phenyl-C(=N)-H, or 1-piperidyloxycarbonyl.

Additionally disclosed are amine compounds of the formula



(X)

where R_1 is:

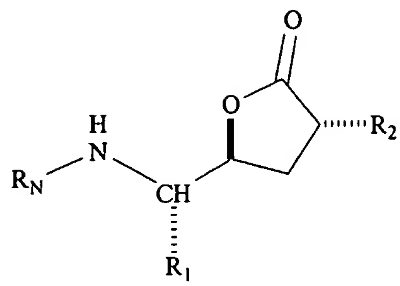
(V) $-CH_2$-phenyl, where phenyl is substituted with two -F in the 3- and 5-positions giving 3, 5-difluorophenyl, or

(VI) $-(CH_2)_{n1}-(R_{1\text{-heteroaryl}})$, where n1 and $R_{1\text{-heteroaryl}}$ are as defined above;

and

where R_2 is as defined in claim 1.

Addtionally disclosed are lactone compounds of the formula



(XI),

where R_1 is:

(I) C_1-C_6 alkyl, unsubstituted or substituted with one, two or three C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, $-NH_2$, -C≡N, $-CF_3$, or $-N_3$,

(II) $-(CH_2)_{1-2}$-S-CH_3,

(III) $-CH_2$-CH_2-S-CH_3,

(IV) $-CH_2$-(C_2-C_6 alkenyl) unsubstituted or substituted by one –F,

(V) $-(CH_2)_{0-3}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-O-CF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) -C≡N,

(VI) $-(CH_2)_{n1}$-($R_{1\text{-heteroaryl}}$) where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,
(G) indolyl,
(H) indolinyl,
(I) pyridazinyl,
(J) pyrazinyl,
(K) isoindolyl,
(L) isoquinolyl,
(M) quinazolinyl,
(N) quinoxalinyl,
(O) phthalazinyl,
(P) imidazolyl,
(Q) isoxazolyl,
(R) pyrazolyl,
(S) oxazolyl,
(T) thiazolyl,
(U) indolizinyl,
(V) indazolyl,
(W) benzothiazolyl,
(X) benzimidazolyl,
(Y) benzofuranyl,
(Z) furanyl,
(AA) thienyl,
(BB) pyrrolyl,
(CC) oxadiazolyl,
(DD) thiadiazolyl,
(EE) triazolyl,
(FF) tetrazolyl,
(GG) 1, 4-benzodioxan
(HH) purinyl,
(II) oxazolopyridinyl,
(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{0\text{-}3}$- by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_3 alkyl,

(2) $-CF_3$,

(3) -F, Cl, -Br, or –I,

(4) C_1-C_3 alkoxy,

(5) $-O-CF_3$,

(6) $-NH_2$,

(7) -OH, or

(8) $-C{\equiv}N$,

with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VII) $-(CH_2)_{n1}-(R_{1\text{-heterocycle}})$ where n_1 is as defined above and

$R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl,

where the $R_{1\text{-heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{-heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or two:

(1) =O,

(2) C_1-C_3 alkyl,

(3) –CF_3,

(4) -F, Cl, -Br and –I,

(5) C_1-C_3 alkoxy,

(6) –O-CF_3,

(7) -NH_2,

(8) -OH, or

(9) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;

where R_2 is:

(I) -H,

(II) C_1-C_6 alkyl, or

(III) $-(CH_2)_{0-4}-R_{2-1}$ where R_{2-1} is (C_3-C_6)cycloalkyl, $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$ where $R_{1\text{-aryl}}$ and $R_{1\text{-heteroaryl}}$ are as defined above,

where R_N is:

(I) $R_{N-1}-X_N-$ where X_N is:

(A) –CO-,

(B) $-SO_2-$,

(C) $-(CR'R'')_{1-6}$ where R' and R" are the same or different and are –H or C_1-C_4 alkyl,

(D) $-CO-(CR'R'')_{1-6}-X_{N-1}$ where X_{N-1} is –O-, -S- and –NR'R"- and where R' and R" are as defined above,

(E) a single bond;

where R_{N-1} is:

(A) $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with one, two, three or four of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1$-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1$-C_6 alkyl unsubstituted or substituted with one to three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_1-C_6 alkenyl with one or two double bonds,

(h) -C_1-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) -$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl$)_2$,

(19) -N-CS-N(C_1-C_3 alkyl$)_2$,

(20) –N(C_1-C_3 alkyl)-CO-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(21) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) $-R_{N-4}$ where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH,

(28) -S-(C_1-C_6 alkyl),

(29) C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F,

(30) –O-(C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F, or

(31) –O-ϕ,

(B) $-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_6 alkyl,

(2) -F, -Cl, -Br, or - I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1$-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1$-C_6 alkyl unsubstituted or substituted with 1, 2, or 3 –F, -Cl, -Br, or -I,

(d) $-C_3$-C_7 cycloalkyl,

(e $-(C_1$-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) $-(C_1$-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) $-C_1$-C_6 alkenyl with one or two double bonds,

(h) $-C_1$-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) -$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(21) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) $-R_{N-4}$ where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH, or

(28) -S-(C_1-C_6 alkyl),

(C) $-R_{N\text{-aryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(D) $-R_{N\text{-aryl}}-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(E) $-R_{N\text{-heteroaryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(F) $-R_{N\text{-heteroaryl}}-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(G) $-R_{N\text{-aryl}}$-O-$R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(H) $-R_{N\text{-aryl}}$-S-$R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(I) $-R_{N\text{-heteroaryl}}$-O-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(J) $-R_{N\text{-heteroaryl}}$-S-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(K) $-R_{N\text{-aryl}}$-CO-$R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(L) $-R_{N\text{-aryl}}$-CO-$R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above,

(M) $-R_{N\text{-aryl}}$-SO_2-$R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(N) $-R_{N\text{-heteroaryl}}$-CO-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(O) $-R_{N\text{-heteroaryl}}$-SO_2-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(P) $-R_{N\text{-aryl}}$-O-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-aryl}}$ is as defined above,

(Q) $-R_{N\text{-aryl}}$-S-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-aryl}}$ is as defined above,

(R) $-R_{N\text{-heteroaryl}}$-O-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-heteroaryl}}$ is as defined above, or

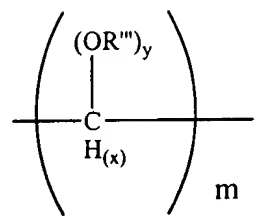
(S) $-R_{N\text{-heteroaryl}}$-S-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-heteroaryl}}$ is as defined above,

(II) A-X_N- where X_N is –CO-,

wherein A is

(A) -T-E-(Q)m',

(1) where -T is



where

(a) x =1 when y = 1 and x = 2 when y = 0,

(b) m is 0, 1, 2 or 3,

(c) the values of x and y vary independently on each carbon when m is 2 and 3, and

(d) R''' varies independently on each carbon and is H, (C1-C2) alkyl, phenyl, or phenyl(C1-C3)alkyl;

(2) -E is

(a) C_1-C_5 alkyl, but only if m' does not equal 0,

(b) methylthioxy(C_2-C_4)alkyl,

(c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,

(f) biphenyl,

(g) diphenyl ether,

(h) diphenylketone,

(i) phenyl(C_1-C_8)alkyloxyphenyl, or

(j) C_1-C_6 alkoxy;

(3) -Q is

(a) C_1-C_3 alkyl,

(b) C_1-C_3 alkoxy,

(c) C_1-C_3 alkylthioxy,

(d) C_1-C_6 alkylacylamino,

(e) C_1-C_6 alkylacyloxy,

(f) amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary amino moieties),

(g) C_1-C_6 alkylamino

(h) phenylamino,

(i) carbamyl (including C_1-C_6 alkyl and phenyl amides and esters),

(j) carboxyl (including C_1-C_6 alkyl and phenyl esters),

(k) carboxy(C_2-C_5)alkoxy,

(l) carboxy(C_2-C5)alkylthioxy,

(m) heterocyclylacyl,

(n) heteroarylacyl, or

(o) hydroxyl;

(4) m' is 0, 1, 2 or 3;

(B) $-E(Q)_{m''}$ wherein E and -Q are as defined as above and m" is 0, 1, 2, or 3;

(C) -T-E wherein -E and -Q are as defined as above; or

(D) -E wherein -E is as defined as above;

(III) –CO-(C_1-C_6 alkyl) where alkyl is unsubstituted or substituted with one or two:

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-N$R_{N-2}$$R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-N$R_{N-2}$$R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -N$R_{N-2}$$R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-N$R_{N-8}$$R_{N-8}$ where the R_{N-8} is the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(IV) –CO-(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-N$R_{N-2}$$R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(V) –CO-(C_1-C_3 alkyl)-S-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) $-SO_2$-(C_1-C_8 alkyl),

(H) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(VI) –CO-CH(-(CH_2)$_{0-2}$-O-R_{N-10})-(CH_2)$_{0-2}$-R_{N-aryl}/$R_{N-heteroaryl}$) where R_{N-aryl} and $R_{N-heteroaryl}$ are as defined above, where R_{N-10} is:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

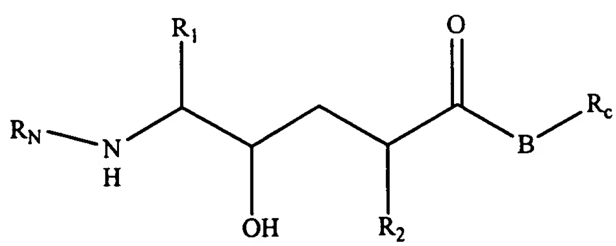
(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) R_{1-aryl} where R_{1-aryl} is as defined above, or

(G) $R_{N-heteroaryl}$ where $R_{N-heteroaryl}$ is as defined above.

Disclosed is a method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from Alzheimer's disease, mild cognitive impairment, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, degenerative dementia, diffuse Lewy body type of Alzheimer's disease or central or peripheral amyloid diseases and who is in need of such treatment which comprises administration of a therapeutically effective amount of a hydroxyethylene compound of formula (XII)



(XII)

where R_1 is:

(I) C_1-C_6 alkyl, unsubstituted or substituted with one, two or three C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -NH_2, -C≡N, -CF_3, or -N_3,

(II) –(CH_2)$_{1-2}$-S-CH_3,

(III) –CH_2-CH_2-S-CH_3,

(IV) -CH_2-(C_2-C_6 alkenyl) unsubstituted or substituted by one –F,

(V) $-(CH_2)_{0-3}-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-O-CF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) -C≡N,

(VI) $-(CH_2)_{n1}-(R_{1\text{-heteroaryl}})$ where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{0\text{-}3}-$ by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_3 alkyl,

(2) $-CF_3$,

(3) -F, Cl, -Br, or –I,

(4) C_1-C_3 alkoxy,

(5) $-O-CF_3$,

(6) $-NH_2$,

(7) -OH, or

(8) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VII) $-(CH_2)_{n1}-(R_{1\text{-heterocycle}})$ where n_1 is as defined above and $R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl,

where the $R_{1\text{-heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{-heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or two:

(1) =O,

(2) C_1-C_3 alkyl,

(3) $-CF_3$,

(4) -F, Cl, -Br and –I,

(5) C_1-C_3 alkoxy,

(6) $-O-CF_3$,

(7) $-NH_2$,

(8) -OH, or

(9) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;

where R_2 is:

(I) -H,

(II) C_1-C_6 alkyl, or

(III) $-(CH_2)_{0-4}-R_{2-1}$ where R_{2-1} is $(C_3$-$C_6)$cycloalkyl, $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$ where $R_{1\text{-aryl}}$ and $R_{1\text{-heteroaryl}}$ are as defined above,

where R_N is:

(I) $R_{N-1}-X_N-$ where X_N is:

(A) –CO-,

(B) $-SO_2-$,

(C) $-(CR'R'')_{1-6}$ where R' and R" are the same or different and are –H or C_1-C_4 alkyl,

(D) $-CO-(CR'R'')_{1-6}-X_{N-1}$ where X_{N-1} is –O-, -S- and –NR'R"- and where R' and R" are as defined above,

(E) a single bond;

where R_{N-1} is:

(A) $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with one, two, three or four of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) -NO_2,

(5) -CO-OH,

(6) -C≡N,

(7) -CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) -C_1-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) -NH_2,

(c) -C_1-C_6 alkyl unsubstituted or substituted with one to three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_1-C_6 alkenyl with one or two double bonds,

(h) -C_1-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) -$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl$)_2$,

(19) -N-CS-N(C_1-C_3 alkyl$)_2$,

(20) –N(C_1-C_3 alkyl)-CO-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is as defined above,

(21) -$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ can be the same or different and are as defined above,

(22) -$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl$)_2$,

(25) -O-CS-N(C_1-C_3 alkyl$)_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH,

(28) -S-(C_1-C_6 alkyl),

(29) C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F,

(30) –O-(C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F, or

(31) –O-ϕ,

(B) -$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,

(Z) furanyl,

(AA) thienyl,

(BB) pyrrolyl,

(CC) oxadiazolyl,

(DD) thiadiazolyl,

(EE) triazolyl,

(FF) tetrazolyl,

(GG) 1, 4-benzodioxan

(HH) purinyl,

(II) oxazolopyridinyl,

(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or - I,

(3) -OH,

(4) -NO_2,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1-C_6$ alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1-C_6$ alkyl unsubstituted or substituted with 1, 2, or 3 –F, -Cl, -Br, or -I,

(d) $-C_3-C_7$ cycloalkyl,

(e $-(C_1-C_2$ alkyl$)-(C_3-C_7$ cycloalkyl),

(f) $-(C_1-C_6$ alkyl)-O-$(C_1-C_3$ alkyl),

(g) $-C_1-C_6$ alkenyl with one or two double bonds,

(h) $-C_1-C_6$ alkynyl with one or two triple bonds,

(i) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) $-CO-(C_3-C_{12}$ alkyl),

(9) $-CO-(C_3-C_6$ cycloalkyl),

(10) $-CO-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) $-CO-R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) $-CO-R_{N-4}$ where R_{N-4} is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or

pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-R_{N-5} where R_{N-5} is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-R_{N-5} where R_{N-5} is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-R_{N-5} where R_{N-5} is as defined above,

(21) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) -R_{N-4} where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH, or

(28) -S-(C_1-C_6 alkyl),

(C) -$R_{N\text{-aryl}}$-$R_{N\text{-aryl}}$ where -$R_{N\text{-aryl}}$ is as defined above,

(D) -$R_{N\text{-aryl}}$-$R_{N\text{-heteroaryl}}$ where -$R_{N\text{-aryl}}$ and -$R_{N\text{-heteroaryl}}$ are as defined above,

(E) -$R_{N\text{-heteroaryl}}$-$R_{N\text{-aryl}}$ where -$R_{N\text{-aryl}}$ and -$R_{N\text{-heteroaryl}}$ are as defined above,

(F) -$R_{N\text{-heteroaryl}}$-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(G) $-R_{N\text{-aryl}}-O-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(H) $-R_{N\text{-aryl}}-S-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(I) $-R_{N\text{-heteroaryl}}-O-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(J) $-R_{N\text{-heteroaryl}}-S-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(K) $-R_{N\text{-aryl}}-CO-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(L) $-R_{N\text{-aryl}}-CO-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above,

(M) $-R_{N\text{-aryl}}-SO_2-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(N) $-R_{N\text{-heteroaryl}}-CO-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(O) $-R_{N\text{-heteroaryl}}-SO_2-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(P) $-R_{N\text{-aryl}}-O-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(Q) $-R_{N\text{-aryl}}-S-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-aryl}}$ is as defined above,

(R) $-R_{N\text{-heteroaryl}}-O-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above, or

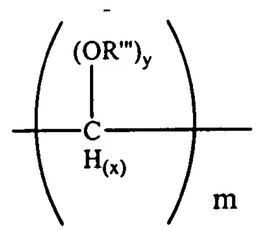
(S) $-R_{N\text{-heteroaryl}}-S-(C_1-C_8\ \text{alkyl})-\phi$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(II) $A-X_N-$ where X_N is –CO-,

wherein A is

(A) $-T-E-(Q)_{m'}$,

(1) where -T is



where

(a) x =1 when y = 1 and x = 2 when y = 0,

(b) m is 0, 1, 2 or 3,

(c) the values of x and y vary independently on each carbon when m is 2 and 3, and

(d) R''' varies independently on each carbon and is H, (C_1-C_2) alkyl, phenyl, or phenyl(C_1-C_3)alkyl;

(2) -E is

(a) C_1-C_5 alkyl, but only if m' does not equal 0,

(b) methylthioxy(C_2-C_4)alkyl,

(c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,

(f) biphenyl,

(g) diphenyl ether,

(h) diphenylketone,

(i) phenyl(C_1-C_8)alkyloxyphenyl, or

(j) C_1-C_6 alkoxy;

(3) -Q is

(a) C_1-C_3 alkyl,

(b) C_1-C_3 alkoxy,

(c) C_1-C_3 alkylthioxy,

(d) C_1-C_6 alkylacylamino,

(e) C_1-C_6 alkylacyloxy,

(f) amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary amino moieties),

(g) C_1-C_6 alkylamino

(h) phenylamino,

(i) carbamyl (including C_1-C_6 alkyl and phenyl amides and esters),

(j) carboxyl (including C_1-C_6 alkyl and phenyl esters),

(k) carboxy(C_2-C_5)alkoxy,

(l) carboxy(C_2-C5)alkylthioxy,

(m) heterocyclylacyl,

(n) heteroarylacyl, or

(o) hydroxyl;

(4) m' is 0, 1, 2 or 3;

(B) -E(Q)$_{m''}$ wherein E and -Q are as defined as above and m" is 0, 1, 2, or 3;

(C) -T-E wherein -E and -Q are as defined as above; or

(D) -E wherein -E is as defined as above;

(III) –CO-(C_1-C_6 alkyl) where alkyl is unsubstituted or substituted with one or two:

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-N$R_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-N$R_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} is the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(IV) –CO-(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(V) –CO-(C_1-C_3 alkyl)-S-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(VI) –CO-CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$-$R_{N\text{-aryl}}$/$R_{N\text{-heteroaryl}}$) where $R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above, where R_{N-10} is:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) $R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(G) $R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above;

where B is -O-, -NH-, or -N(C_1-C_6 alkyl)-;

where R_C is:

(I) -(C_1-C_{10})alkyl-K_{1-3} in which:

(A) the alkyl chain is unsubstituted or substituted with one –OH,

(B) the alkyl chain is unsubstituted or substituted with one C_1-C_6 alkoxy unsubstituted or substituted with 1-5 -F,

(C) the alkyl chain is unsubstituted or substituted with one –O-ϕ,

(D) the alkyl chain is unsubstituted or substituted with 1-5 –F,

(E) the alkyl chain is unsubstituted or substituted with a combination of up to three atoms of oxygen and sulfur each such atom replacing one carbon,

(F) each K is:

(1) H,

(2) C_1-C_3 alkyl,

(3) C_1-C_3 alkoxy,

(4) C_1-C_3 alkylthioxy,

(5) C_1-C_6 alkylacylamino,

(6) C_1-C_6 alkylacyloxy,

(7) amido

(8) C_1-C_6 alkylamino

(9) phenylamino,

(10) carbamyl

(11) carboxyl

(12) carboxy(C_2-C_5)alkoxy,

(13) carboxy(C_2-C5)alkylthioxy,

(14) heterocyclylacyl,

(15) heteroarylacyl,

(16) amino unsubstituted or substituted with C_1-C_6 alkyl,

(17) hydroxyl, or

(18) carboxyl methyl ester;

(II)-$(CH_2)_{0\text{-}3}$-J-[(-$(CH_2)_{0\text{-}3}$-K]$_{1\text{-}3}$ where K is as defined above and J is:

(A) a 5 to 7 atom monocyclic aryl group,

(B) a 8 to 12 atom multicyclic aryl group,

(C) a 5 to 7 atom heterocyclic group,

(D) a 8 to 12 atom multicyclic heterocyclic group, or

(E) a 5 to 10 atom monocyclic or multicyclic cycloalkyl group;

(III) -$(CH_2)_{0-3}$-(C_3-C_7) cycloalkyl where cycloalkyl can be unsubstituted or substituted with one, two or three

(A) C_1-C_3 alkyl unsubstituted or substituted with 1, 2, 3, or 4 –F, -Cl, -Br, or -I,

(B) -CO-OH,

(C) -CO-O-(C_1-C_4 alkyl),

(D) -OH, or

(E) C_1-C_6 alkoxy,

(IV) -$(CH_2)_{2-6}$-OH,

(V) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are –H, C_1-C_4 alkyl and ϕ- and R_{C-aryl} is the same as R_{N-aryl},

(VI) -$(CH_2)_{0-4}$-$R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) isoxazolyl,

(Q) pyrazolyl,

(R) indolizinyl,

(S) indazolyl,

(T) benzothiazolyl,

(U) benzimidazolyl,

(V) benzofuranyl,

(W) furanyl,

(X) thienyl,

(Y) pyrrolyl,

(Z) oxadiazolyl,

(AA) thiadiazolyl,

(BB) triazolyl,

(CC) tetrazolyl,

(DD) 1, 4-benzodioxan

(EE) purinyl,

(FF) oxazolopyridinyl,

(GG) imidazopyridinyl,

(HH) isothiazolyl,

(II) naphthyridinyl,

(JJ) cinnolinyl,

(KK) carbazolyl,

(LL) β-carbolinyl,

(MM) isochromanyl,

(NN) chromanyl,

(OO) furazanyl,

(PP) tetrahydroisoquinoline,

(QQ) isoindolinyl,

(RR) isobenzotetrahydrofuranyl,

(SS) isobenzotetrahydrothienyl,

(TT) isobenzothiophenyl,

(UU) benzoxazolyl, or

(VV) pyridopyridinyl,

(VII) $-(CH_2)_{0-4}-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is the same as $R_{1\text{-heterocycle}}$,

(VIII) $-C(R_{C-1})(R_{C-2})-CO-NH-R_{C-3}$ where R_{C-1} and R_{C-2} are the same or different and are:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-(C_1-C_4$ alkyl$)-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above for $R_{1\text{-aryl}}$,

(D) $-(C_1-C_4$ alkyl$)-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) $-(C_1-C_4$ alkyl$)-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(G) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(H) $-(CH_2)_{1-4}-OH$,

(I) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C'\text{-aryl}}$ where R_{C-4} is –O–, -S-, -NH- or $-NHR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl, and where $R_{C'\text{-aryl}}$ is as defined above,

(J) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{1-4}-R_{C\text{-heteroaryl}}$ where R_{C-4} and $R_{C\text{-heteroaryl}}$ are as defined above, or

(K) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

and where R_{C-3} is:

(A) -H,

(B) $-C_1-C_6$ alkyl,

(C) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(D) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) $-(C_1-C_4$ alkyl$)-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(G) $-(C_1-C_4$ alkyl$)-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above, or

(H) -(C_1-C_4 alkyl)-$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(IX) -CH(ϕ)$_2$,

(X) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one, two or three:

(A) C_1-C_3 alkyl,

(B) –CF_3,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) -OCF_3,

(F) -NH_2,

(G) -OH, or

(H) -C≡N,

(XI) –CH_2-C≡CH;

(XII) –$(CH_2)_{0\text{-}1}$-CH$R_{C\text{-}5}$-$(CH_2)_{0\text{-}1}$-ϕ where $R_{C\text{-}5}$ is:

(A) –OH, or

(B)-CH_2-OH;

(XIII) –CH(-ϕ)-CO-O(C_1-C_3 alkyl);

(XIV) –CH(-CH_2-OH)-CH(-OH)-ϕ-NO_2;

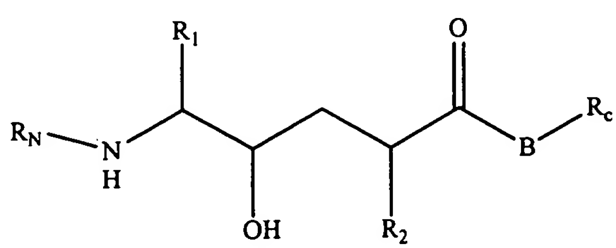
(XV) –$(CH_2)_2$-O-$(CH_2)_2$-OH;

(XVI) –CH_2-NH-CH_2-CH(-O-CH_2-CH_3)$_2$;

(XVII) -(C_2-C_8) alkynyl; or

(XVIII) –H; or a pharmaceutically acceptable salt thereof.

Disclosed is the use of a hydroxyethylene compound of formula (XII)



(XII)

where R_1, R_2, R_C, and R_N are as defined immediately above, and pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from Alzheimer's disease, mild cognitive impairment, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, degenerative dementia, diffuse Lewy body type of Alzheimer's disease or central or preipheral amyloid diseases and who is in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides hydroxyethylene compounds of formula (XII) which are useful in treating and preventing Alzheimer's disease. The anti-Alzheimer's hydroxyethylene compounds of formula (XII) are made by methods well known to those skilled in the art from starting compounds known to those skilled in the art. The process chemistry is well known to those skilled in the art. The most general process to prepare the hydroxyethylene compounds of formula (XII) is set forth in CHART A, as defined within. The chemistry is straight forward and in summary involves the steps of N-protecting an amino acid (I) starting material to produce the corresponding protected amino acid (II), amino-dehydroxylation of the protected amino acid (II) with the appropriate amine in the presence of a coupling agent to produce the corresponding protected amide (III), reduction of the protected amide to the corresponding aldehyde (IV), formation of the terminal olefin as described (V), peracid epoxidation of the olefin (V) to produce the corresponding epoxide (VI), opening of the epoxide (VI) with an amide (VII) to produce the corresponding protected alcohol (VIII), cyclization of the protected alcohol (VIII) to produce the protected lactone (IX) which then has the nitrogen protecting group removed to produce the corresponding amine (X), which is then reacted with an amide forming agent of the formula $(R_{N-1}\text{-}X_N)_2O$ or $R_{N-1}\text{-}X_N\text{-}X_2$ or $R_{N-1}\text{-}X_N\text{-}OH$, for example, to produce the lactone (XI), opening of the lactone (XI) with a C-terminal amine, $R_C\text{-}NH_2$ to produce the anti-Alzheimer hydroxyethylene compounds of formula (XII). One skilled in the art will appreciate that these are all well known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical

structure of the biologically active hydroxyethylene compounds of formula (XII) would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the present invention.

The backbone of the compounds of the present invention is a hydroxyethylene moiety. It can be readily prepared by methods disclosed in the literature and known to those skilled in the art. For example, Henning, R. "Synthetic Routes to Different Classes of Natural Products and Analogs Thereof. Synthesis of Hydroxyethylene Isosteric Dipeptides." In Organic Synthesis Highlights II; VCH: Weinheim, Germany, 1995; pp 251-259 discloses processes to prepare hydroxyethylene type compounds.

CHART A, as defined within, sets forth a general method used in the present invention to prepare the appropriately substituted hydroxyethylene compounds of formula (XII). The anti-Alzheimer hydroxyethylene compounds of formula (XII) are prepared by starting with the corresponding amino acid (I). The amino acids (I) are well known to those skilled in the art or can be readily prepared from known compounds by methods well known to those skilled in the art. The hydroxyethylene compounds of formula (XII) have at least three enantiomeric centers which give 8 enantiomers, the S, S, R stereochemistry being preferred. The first of these enantiomeric centers derives from the amino acid starting material (I). It is preferred to commercially obtain or produce the desired enantiomer (S) rather than produce an enantiomerically impure mixture and then have to separate out the desired enantiomer (S). It is preferred to start the process with enantiomerically pure (S)-amino acid (I) of the same configuration as that of the hydroxyethylene product. For the amino acids (I), R_1 is:

(I) C_1-C_6 alkyl, unsubstituted or substituted with one, two or three C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, $-NH_2$, $-C\equiv N$, $-CF_3$, or $-N_3$,

(II) $-(CH_2)_{1-2}-S-CH_3$,

(III) $-CH_2-CH_2-S-CH_3$,

(IV) $-CH_2-(C_2-C_6$ alkenyl) unsubstituted or substituted by one –F,

(V) $-(CH_2)_{0-3}-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-O-CF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) -C≡N,

(VI) $-(CH_2)_{n1}-(R_{1\text{-heteroaryl}})$ where n_1 is 0, 1, 2, or 3 and $R_{1\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,
(T) thiazolyl,
(U) indolizinyl,
(V) indazolyl,
(W) benzothiazolyl,
(X) benzimidazolyl,
(Y) benzofuranyl,
(Z) furanyl,
(AA) thienyl,
(BB) pyrrolyl,
(CC) oxadiazolyl,
(DD) thiadiazolyl,
(EE) triazolyl,
(FF) tetrazolyl,
(GG) 1, 4-benzodioxan
(HH) purinyl,
(II) oxazolopyridinyl,
(JJ) imidazopyridinyl,
(KK) isothiazolyl,
(LL) naphthyridinyl,
(MM) cinnolinyl,
(NN) carbazolyl,
(OO) β-carbolinyl,
(PP) isochromanyl,
(QQ) chromanyl,
(RR) furazanyl,
(SS) tetrahydroisoquinoline,
(TT) isoindolinyl,
(UU) isobenzotetrahydrofuranyl,
(VV) isobenzotetrahydrothienyl,
(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{0\text{-}3}$- by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_3 alkyl,

(2) $-CF_3$,

(3) -F, Cl, -Br, or –I,

(4) C_1-C_3 alkoxy,

(5) $-O-CF_3$,

(6) $-NH_2$,

(7) -OH, or

(8) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VII) $-(CH_2)_{n1}-(R_{1\text{-heterocycle}})$ where n_1 is as defined above and

$R_{1\text{-heterocycle}}$ is:

(A) morpholinyl,

(B) thiomorpholinyl,

(C) thiomorpholinyl S-oxide,

(D) thiomorpholinyl S,S-dioxide,

(E) piperazinyl,

(F) homopiperazinyl,

(G) pyrrolidinyl,

(H) pyrrolinyl,

(I) tetrahydropyranyl,

(J) piperidinyl,

(K) tetrahydrofuranyl, or

(L) tetrahydrothiophenyl,

where the $R_{1\text{-heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{-heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or two:

(1) =O,

(2) C_1-C_3 alkyl,

(3) $-CF_3$,

(4) -F, Cl, -Br and –I,

(5) C_1-C_3 alkoxy,

(6) $-O-CF_3$,

(7) $-NH_2$,

(8) -OH, or

(9) -C≡N,

with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen. Typically, R_1 is (V) $-(CH_2)_{0-1}-(R_{1\text{-aryl}})$ or (VI) $-(CH_2)_{n1}-(R_{1\text{-heteroaryl}})$. It is preferred that R_1 is (V) $-(CH_2)-(R_{1\text{-aryl}})$ or (VI) $-(CH_2)-(R_{1\text{-heteroaryl}})$. It is more preferred that R_1 is $-(CH_2)-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is phenyl. It is even more preferred that R_1 is $-(CH_2)-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is phenyl substituted with two –F. It is most preferred that the –F substitution is 3,5 on the phenyl ring.

When R_1 is $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ the bond from the $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group to the $-(CH_2)_{n1}-$ group can be from any ring atom which has an available valence provided that such bond does not result in formation of a charged species or unstable valence. This means that the $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group is bonded to $-(CH_2)_{n1}-$by any ring atom of the parent $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group which was substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group replaces the hydrogen atom and its bond.

The first step of the process is to protect the free amino group of the (S)-amino acid (I) with an amino protecting group to produce the (S)-protected amino acid (II) by methods well known to those skilled in the art. Amino protecting groups are well known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 2nd ed., 1991, Chapter 7; "Protecting Groups in

Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. The function of the amino protecting group is to protect the free amino functionality ($-NH_2$) during subsequent reactions on the (S)-amino acid (I) which would not proceed well either because the amino group would react and be functionalized in a way that is inconsistent with its need to be free for subsequent reactions or the free amino group would interfere in the reaction. When the amino protecting group is no longer needed, it is removed by methods well known to those skilled in the art. By definition the amino protecting group must be readily removable as is known to those skilled in the art by methods well known to those skilled in the art. Suitable amino PROTECTING GROUPs include *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxazoylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl, -phenyl-C(=N)-H, and 1-piperidyloxycarbonyl. It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will understand the preferred methods of introducing a *t*-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 2nd ed., 1991, at 327-335 for guidance.

The (S)-protected amino acid (II) is transformed to the corresponding (S)-protected amide compound (III) by means well known to those skilled in the art for the production of an amide from a carboxylic acid and an amine or hydroxylamine. The means and reaction conditions for producing the (S)-protected amide compound (III) include, for example, the use of a coupling agent such as, for example, dicyclohexylcarbodiimide, 1,1-carbonyldiimidazole, $POCl_3$, $TiCl_4$, SO_2ClF, benzotriazol-1-yl diethyl phosphate, or N, N, N', N'-tetramethyl(succinimido)uronium tetrafluoroborate in the presence of an amine or hydroxylamine. 1,1-Carbonyldiimidazole is a preferred coupling agent and N-methyl-O-methylhydroxylamine is a preferred hydroxylamine. The reaction is carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78^{o} to elevated temperature up to the reflux point of the solvent employed. It is preferred to conduct the reaction between 0^{o} and 50^{o}.

The (S)-protected amide compound (III) is then reduced by means well known to those skilled in the art for reduction of a amide to the corresponding aldehyde, affording the corresponding aldehyde (IV). The means and reaction conditions for reducing the (S)-protected amide compound (III) to the corresponding aldehyde (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Lithium aluminium hydride is the preferred reducing agent. The reductions are carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78^{o} to room temperature. It is preferred to conduct the reduction between -20^{o} and room temperature. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, VCH Publishers, 1989.

The aldehyde (IV) is transformed to the corresponding olefin (V) by means known to those skilled in the art. An example of such a reaction is the reaction of the aldehyde (IV) with a phosphorous ylide to produce the desired olefin. Such phosphorous ylides include methyltriphenylphosphonium bromide. Reaction conditions include

temperatures ranging from -100^{o} up to the reflux temperature of the solvent employed; preferred temperature ranges are between -100^{o} and $0°$.

Peracid epoxidation of the olefin (V) affords the epoxide (VI). Other methods for the conversion of an olefin to an epoxide are known to those skilled in the art. The means for producing the epoxide (VI) include, for example, the use of a peracid such as, for example, peracetic acid, perbenzoic, trifluoroperacetic acid, 3,5-dinitroperoxybenzoic acid, and m-chloroperbenzoic acid.

The epoxide (VI) is then reacted with the appropriate amide (VII) by means known to those skilled in the art which opens the epoxide to produce the desired corresponding protected alcohol (VIII). Reaction of the epoxide (VI) with the amide (VII) produces a mixture of enantiomers. This enantiomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, most preferably by HPLC, employing commercially available chiral columns. The enantiomer that is used in the remainder of the process of CHART A is the (S,S, R)-alcohol (VIII).

The protected-alcohol (VIII) is transformed to the corresponding protected lactone (IX) by means known to those skilled in the art. A preferred means is by reaction with an acid catalyst, for example, but not limited to, p-toluenesulfonic acid and the like. Reactions are conducted at temperatures ranging from -78^{o} up to the reflux temperature of the solvent employed; preferred temperature ranges are between 0^{o} and $50°$.

The amine moiety or the protected lactone (IX) is deprotected to the corresponding amine (X) by means known to those skilled in the art for removal of amine protecting group. Suitable means for removal of the amine protecting group depends on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group, know which reagent is preferable for its removal. For example, it is preferred to remove the preferred protecting group, BOC, by dissolving the protected lactone (IX) in a trifluoroacetic acid/dichloromethane mixture. When complete, the solvents are removed under reduced pressure to give the corresponding lactone (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if desired, the lactone can be purified further by means well known to those skilled in the art, such as for example, recrystallization. Further, if the

non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991, p. 309 and following. Chemically suitable salts include trifluoroacetate, and the anion of mineral acids such as chloride, sulfate, phosphate; preferred is trifluoroacetate.

The amine (X) is then reacted with an appropriately substituted-amide-forming-agent such as anhydride, acyl halide, or acid of the formula $(R_{N-1}\text{-}X_N)_2O$ or $R_{N-1}\text{-}X_N\text{-}X_2$ or $R_{N-1}\text{-}X_N\text{-}OH$ by nitrogen-acylation means known to those skilled in the art to produce the corresponding lactone (XI). Nitrogen acylation conditions for reaction of the amine (X) with an amide forming agent to produce the corresponding lactone (XI) are known to those skilled in the art and can be found in R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972. R_N includes:

(I) $R_{N-1}\text{-}X_N\text{-}$ where X_N is:

(A) –CO-,

(B) $–SO_2$-,

(C) $-(CR'R'')_{1-6}$ where R' and R" are the same or different and are –H or C_1-C_4 alkyl,

(D) $–CO-(CR'R'')_{1-6}-X_{N-1}$ where X_{N-1} is –O-, -S- and –NR'R"- and where R' and R" are as defined above,

(E) a single bond;

where R_{N-1} is:

(A) $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with one, two, three or four of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or -I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) -CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) -C_1-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) -NH_2,

(c) -C_1-C_6 alkyl unsubstituted or substituted with one to three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_1-C_6 alkenyl with one or two double bonds,

(h) -C_1-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) -$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) -$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) -CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) -CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) -CO-R_{N-4} where R_{N-4} is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) -CO-O-R_{N-5} where R_{N-5} is:

(a) C_1-C_6 alkyl, or

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(14) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(15) -SO-(C_1-C_8 alkyl),

(16) -SO_2-(C_3-C_{12} alkyl),

(17) -NH-CO-O-R_{N-5} where R_{N-5} is as defined above,

(18) -NH-CO-N(C_1-C_3 alkyl)$_2$,

(19) -N-CS-N(C_1-C_3 alkyl)$_2$,

(20) –N(C_1-C_3 alkyl)-CO-R_{N-5} where R_{N-5} is as defined above,

(21) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) -R_{N-4} where R_{N-4} is as defined above,

(23) –O-CO-(C_1-C_6 alkyl),

(24) -O-CO-N(C_1-C_3 alkyl)$_2$,

(25) -O-CS-N(C_1-C_3 alkyl)$_2$,

(26) -O-(C_1-C_6 alkyl),

(27) -O-(C_2-C_5 alkyl)-COOH,

(28) -S-(C_1-C_6 alkyl),

(29) C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F,

(30) –O-(C_1-C_6 alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 –F, or

(31) –O-ϕ,

(B) -$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,
(G) indolyl,
(H) indolinyl,
(I) pyridazinyl,
(J) pyrazinyl,
(K) isoindolyl,
(L) isoquinolyl,
(M) quinazolinyl,
(N) quinoxalinyl,
(O) phthalazinyl,
(P) imidazolyl,
(Q) isoxazolyl,
(R) pyrazolyl,
(S) oxazolyl,
(T) thiazolyl,
(U) indolizinyl,
(V) indazolyl,
(W) benzothiazolyl,
(X) benzimidazolyl,
(Y) benzofuranyl,
(Z) furanyl,
(AA) thienyl,
(BB) pyrrolyl,
(CC) oxadiazolyl,
(DD) thiadiazolyl,
(EE) triazolyl,
(FF) tetrazolyl,
(GG) 1, 4-benzodioxan
(HH) purinyl,
(II) oxazolopyridinyl,
(JJ) imidazopyridinyl,

(KK) isothiazolyl,

(LL) naphthyridinyl,

(MM) cinnolinyl,

(NN) carbazolyl,

(OO) β-carbolinyl,

(PP) isochromanyl,

(QQ) chromanyl,

(RR) furazanyl,

(SS) tetrahydroisoquinoline,

(TT) isoindolinyl,

(UU) isobenzotetrahydrofuranyl,

(VV) isobenzotetrahydrothienyl,

(WW) isobenzothiophenyl,

(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

(1) C_1-C_6 alkyl,

(2) –F, -Cl, -Br, or - I,

(3) -OH,

(4) $-NO_2$,

(5) -CO-OH,

(6) -C≡N,

(7) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are:

(a) -H,

(b) $-C_1$-C_6 alkyl unsubstituted or substituted with one

(i) -OH, or

(ii) $-NH_2$,

(c) $-C_1-C_6$ alkyl unsubstituted or substituted with 1, 2, or 3 –F, -Cl, -Br, or -I,

(d) $-C_3-C_7$ cycloalkyl,

(e $-(C_1-C_2$ alkyl)-(C_3-C_7 cycloalkyl),

(f) $-(C_1-C_6$ alkyl)-O-(C_1-C_3 alkyl),

(g) $-C_1-C_6$ alkenyl with one or two double bonds,

(h) $-C_1-C_6$ alkynyl with one or two triple bonds,

(i) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) -CO-(C_3-C_{12} alkyl),

(9) -CO-(C_3-C_6 cycloalkyl),

(10) $-CO-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(11) $-CO-R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(12) $-CO-R_{N-4}$ where R_{N-4} is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C_1-C_3 alkyl,

(13) $-CO-O-R_{N-5}$ where R_{N-5} is:

(a) C_1-C_6 alkyl, or

(b) $-(CH_2)_{0-2}-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is as defined above,

(14) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(15) $-SO-(C_1-C_8$ alkyl),

(16) $-SO_2-(C_3-C_{12}$ alkyl),

(17) $-NH-CO-O-R_{N-5}$ where R_{N-5} is as defined above,

(18) $-NH-CO-N(C_1-C_3$ alkyl$)_2$,

(19) $-N-CS-N(C_1-C_3$ alkyl$)_2$,

(20) $-N(C_1-C_3$ alkyl$)-CO-R_{N-5}$ where R_{N-5} is as defined above,

(21) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(22) $-R_{N-4}$ where R_{N-4} is as defined above,

(23) $-O-CO-(C_1-C_6$ alkyl),

(24) $-O-CO-N(C_1-C_3$ alkyl$)_2$,

(25) $-O-CS-N(C_1-C_3$ alkyl$)_2$,

(26) $-O-(C_1-C_6$ alkyl),

(27) $-O-(C_2-C_5$ alkyl)-COOH, or

(28) $-S-(C_1-C_6$ alkyl),

(C) $-R_{N\text{-aryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(D) $-R_{N\text{-aryl}}-R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(E) $-R_{N\text{-heteroaryl}}-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ and $-R_{N\text{-heteroaryl}}$ are as defined above,

(F) $-R_{N\text{-heteroaryl}}-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(G) $-R_{N\text{-aryl}}-O-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(H) $-R_{N\text{-aryl}}-S-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(I) $-R_{N\text{-heteroaryl}}-O-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(J) $-R_{N\text{-heteroaryl}}-S-R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(K) $-R_{N\text{-aryl}}-CO-R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(L) $-R_{N\text{-aryl}}$-CO-$R_{N\text{-heteroaryl}}$ where $-R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above,

(M) $-R_{N\text{-aryl}}$-SO_2-$R_{N\text{-aryl}}$ where $-R_{N\text{-aryl}}$ is as defined above,

(N) $-R_{N\text{-heteroaryl}}$-CO-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(O) $-R_{N\text{-heteroaryl}}$-SO_2-$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above,

(P) $-R_{N\text{-aryl}}$-O-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-aryl}}$ is as defined above,

(Q) $-R_{N\text{-aryl}}$-S-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-aryl}}$ is as defined above,

(R) $-R_{N\text{-heteroaryl}}$-O-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-heteroaryl}}$ is as defined above, or

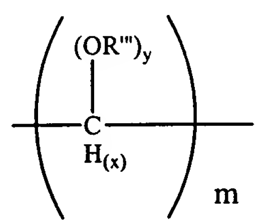
(S) $-R_{N\text{-heteroaryl}}$-S-(C_1-C_8 alkyl)-ϕ where $R_{N\text{-heteroaryl}}$ is as defined above,

(II) A-X_N- where X_N is –CO-,

wherein A is

(A) -T-E-$(Q)_{m'}$,

(1) where -T is



where

(a) x =1 when y = 1 and x = 2 when y = 0,

(b) m is 0, 1, 2 or 3,

(c) the values of x and y vary independently on each carbon when m is 2 and 3, and

(d) R''' varies independently on each carbon and is H, (C_1-C_2) alkyl, phenyl, or phenyl(C_1-C_3)alkyl;

(2) -E is

(a) C_1-C_5 alkyl, but only if m' does not equal 0,

(b) methylthioxy(C_2-C_4)alkyl,

(c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,

(f) biphenyl,

(g) diphenyl ether,

(h) diphenylketone,

(i) phenyl(C_1-C_8)alkyloxyphenyl, or

(j) C_1-C_6 alkoxy;

(3) -Q is

(a) C_1-C_3 alkyl,

(b) C_1-C_3 alkoxy,

(c) C_1-C_3 alkylthioxy,

(d) C_1-C_6 alkylacylamino,

(e) C_1-C_6 alkylacyloxy,

(f) amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary amino moieties),

(g) C_1-C_6 alkylamino

(h) phenylamino,

(i) carbamyl (including C_1-C_6 alkyl and phenyl amides and esters),

(j) carboxyl (including C_1-C_6 alkyl and phenyl esters),

(k) carboxy(C_2-C_5)alkoxy,

(l) carboxy(C_2-C5)alkylthioxy,

(m) heterocyclylacyl,

(n) heteroarylacyl, or

(o) hydroxyl;

(4) m' is 0, 1, 2 or 3;

(B) $-E(Q)_{m''}$ wherein E and -Q are as defined as above and m'' is 0, 1, 2, or 3;

(C) -T-E wherein -E and -Q are as defined as above; or

(D) -E wherein -E is as defined as above;

(III) $-CO-(C_1-C_6$ alkyl) where alkyl is unsubstituted or substituted with one or two:

(A) -OH,

(B) $-C_1-C_6$ alkoxy,

(C) $-C_1-C_6$ thioalkoxy,

(D) $-CO-O-R_{N-8}$ where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) $-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) $-CO-R_{N-4}$ where R_{N-4} is as defined above,

(G) $-SO_2-(C_1-C_8$ alkyl),

(H) $-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) $-NH-CO-(C_1-C_6$ alkyl),

(J) $-NH-CO-O-R_{N-8}$ where R_{N-8} is as defined above,

(K) $-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) $-R_{N-4}$ where R_{N-4} is as defined above,

(M) $-O-CO-(C_1-C_6$ alkyl),

(N) $-O-CO-NR_{N-8}R_{N-8}$ where the R_{N-8} is the same or different and are as defined above, or

(O) $-O-(C_1-C_5$ alkyl)-COOH,

(IV) –CO-(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(V) –CO-(C_1-C_3 alkyl)-S-(C_1-C_3 alkyl) where alkyl is unsubstituted or substituted with one or two

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -ϕ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8} are the same or different and are as defined above, or

(O) -O-(C_1-C_5 alkyl)-COOH,

(VI) –CO-CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$-$R_{N\text{-aryl}}$/$R_{N\text{-heteroaryl}}$) where $R_{N\text{-aryl}}$ and $R_{N\text{-heteroaryl}}$ are as defined above, where R_{N-10} is:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) $R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, or

(G) $R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is as defined above.

It is preferred that R_N is R_{N-1}-X_N- where X_N is –CO-, where R_{N-1} is $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl substituted with one -CO-$NR_{N-2}R_{N-3}$ where the substitution on phenyl is 1,3-,

R_{N-1}-X_N- where X_N is–CO-, where R_{N-1} is $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl substituted with one C_1 alkyl and with one -CO-$NR_{N-2}R_{N-3}$ where the substitution on the phenyl is 1,3,5-, or

R_{N-1}-X_N- where X_N is –CO-, where R_{N-1} is $R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is substituted with one -CO-$NR_{N-2}R_{N-3}$. It is further preferred that R_{N-2} and R_{N-3} are the same and are C_3 alkyl.

It is further preferred that:

R_{N-1}-X_N- where X_N is –CO-, where R_{N-1} is $R_{N\text{-aryl}}$ where $R_{N\text{-aryl}}$ is phenyl substituted with one -CO-$NR_{N-2}R_{N-3}$ where the substitution on phenyl is 1,3-,

R_{N-1}-X_N- where X_N is–CO-, where R_{N-1} is R_{N-aryl} where R_{N-aryl} is phenyl substituted with one C_1 alkyl and with one -CO-$NR_{N-2}R_{N-3}$ where the substitution on the phenyl is 1,3,5-.

It is preferred that X_N is (A) –CO- and (B) –SO_2-; it is more preferred that X_N be -CO-.

The nitrogen-acylation of primary amines to produce secondary amides is one of the oldest known reactions. The amide forming agents, $(R_{N-1}\text{-}X_N)_2O$ or R_{N-1}-X_N-X_2 or R_{N-1}-X_N-OH are known to those skilled in the art and are commercially available or can be readily prepared from known starting materials by methods known in the literature. X_2 includes –Cl, -Br; it is preferred that X_2 is –Cl. It is preferred to use an isophthalic acid acylating agent of the formula $R_{N-2}R_{N-3}$N-CO-ϕ-CO- or a methylisophthalic acid acylating agent $R_{N-2}R_{N-3}$N-CO-(CH_3-)ϕ-CO- where the substitution is 5-methyl-1,3-isophthalic acid. The more preferred 5-methyl-1,3-isophthalic acid is 3-[(N,N-dipropylamino)carbonyl]-5-methylbenzoic acid. These compounds are preferably prepared as set forth as follows. An ester, preferably the methyl ester of isophthalate or methyl 5-methyl-1,3-isophthalate is dissolved in a THF/DMF mixture. 1,1'-Carbonyldiimidazole is then added at 0-100°. Next the desired amine (H-$NR_{N-2}R_{N-3}$) is added. After stirring at 0-100° the reaction mixture is partitioned between a saturated aqueous solution with a pH of 3 to 9 and a water immiscible organic solvent. The aqueous layer is separated and extracted twice more with the organic solvent. The organic extracts are combined and then washed with an aqueous solution and dried. Filtration of the drying agent and removal of solvents by reduced pressure gives crude ester of the desired $R_{N-2}R_{N-3}$N-CO-ϕ-CO-O-CH_3 or a methylisophthalic acid acylating agent $R_{N-2}R_{N-3}$N-CO-(CH_3-)ϕ-CO-O-CH_3.- Purification of the ester can be achieved via chromatography on silica gel eluting with a suitable solvent The isophthalate ester or methylisophthalate ester of the mono-alkyl or di-alkyl amide is then treated with an aqueous solution of base such as alkali hydroxide in a minimum amount of THF/methanol/water and stirred at 20-70° with monitoring. The solvents are removed under reduced pressure and subsequently partitioned between water and a water immiscible organic solvent. The aqueous phase is separated and extracted once more with a water immiscible organic solvent. The aqueous phase was then acidified to

$pH \leq 3$. The mixture obtained is then extracted three times with ethyl acetate. These combined organic extracts are then dried. The drying agent is removed by filtration and the organic solvent remove under reduced pressure to gave crude product. The crude mono- or di-alkyl amide isophthalate/methylisophthalate is used as such in the next reaction with the amine (X) to produce the lactone (XI).

When it is desired to produce a primary amide, R_{N-2} and R_{N-3} are both –H, the following procedure is preferred. An ester of isophthalate or methyl 5-methyl-1,3-isophthalate is dissolved in a THF/DMF mixture. CDI is then added at 0-100°. Ammonia gas is then bubbled into the mixture with monitoring. The reaction is cooled to 0° for the duration of the ammonia addition. The reaction is left stirring under a balloon of ammonia at 0-100° with monitoring. The reaction is partitioned between a aqueous solution with a pH of 3 to 9 and a water immiscible organic solvent. The phases are separated and the aqueous phase is extracted twice more with a water immiscible organic solvent. The organic extracts are washed with an aqueous solution and dried. Removal of solvents under reduced pressure gives crude ester of the desired H_2N-CO-ϕ-CO-O(Alkyl) or a methylisophthalic acid acylating agent H_2N-CO-(CH_3-)ϕ-CO-O(Alkyl). Purification of the crude ester can be achieved via chromatography on silica gel eluting with isopropanol/chloroform. The isophthalate ester or methylisophthalate ester of the primary amide is then treated with an aqueous solution of base such as alkali hydroxide in a minimum amount of THF/methanol/water and stirred at 0-100° with monitoring. The solvents are removed under reduced pressure and subsequently partitioned between water and a water immiscible organic solvent. The aqueous phase is separated and extracted once more with a water immiscible organic solvent. The aqueous phase is then acidified until $pH \leq 3$. The mixture obtained is then extracted three times with a water immiscible organic solvent. These combined organic extracts are dried and the organic solvent removed under reduced pressure to gave crude product. The primary amide isophthalate/methylisophthalate is used as such in the next reaction with (X) to produce (XI).

When it is desired that the amine be cyclized to be a group such as morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl, etc the following procedure is followed. An ester of isophthalate or methyl 5-methyl-1,3-isophthalate is dissolved in a suitable

organic solvent and a catalytic amount or DMF is added. The mixture is cooled to -20° to below rt and then oxalyl chloride is added. The mixture is stirred with monitoring and the solvents removed under reduced pressure. The acid chloride is left under vacuum overnight. The crude acid chloride is dissolved in a suitable organic solvent and cooled to -20° to below rt before the addition of the cyclic amine and N-methyl piperidine. The reaction mixture is stirred at -20° to below rt with monitoring before the solvents are removed. The residue is diluted with water and water immiscible organic solvent and the phases are separated. The aqueous phase is extracted twice more with water immiscible organic solvent, and the combined organic extracts are washed with an aqueous solution and dried. Removal of solvents under reduced pressure gives the crude product. The crude cyclicamide is then treated with an aqueous base such as alkali hydroxide a minimum amount of THF/methanol/water and stirred overnight at 0-100°. The solvents are removed under reduced pressure and subsequently partitioned between water and a water immiscible organic solvent. The aqueous phase is extracted once more with a water immiscible organic solvent. Removal of water from the aqueous phase under reduced pressure gives the desired cyclic amide product.

The lactone (XI) may then be reacted with the appropriately substituted C-terminal amine, R_C-NH_2 by means known to those skilled in the art which opens the lactone to produce the desired hydroxyethylene end product (XII). The substituted C-terminal amines, R_C-NH_2 of this invention are commercially available or are known to those skilled in the art and can be readily prepared from known compounds. R_C includes:

(I) -(C_1-C_{10})alkyl-$K_{1\text{-}3}$ in which:

- (A) the alkyl chain is unsubstituted or substituted with one –OH,
- (B) the alkyl chain is unsubstituted or substituted with one C_1-C_6 alkoxy unsubstituted or substituted with 1-5 -F,
- (C) the alkyl chain is unsubstituted or substituted with one –O-ϕ,
- (D) the alkyl chain is unsubstituted or substituted with 1, 2, 3, 4 or 5 –F,
- (E) the alkyl chain is unsubstituted or substituted with a combination of up to three atoms of oxygen and sulfur each such atom replacing one carbon,

(F) each K is:

(1) H,

(2) C_1-C_3 alkyl,

(3) C_1-C_3 alkoxy,

(4) C_1-C_3 alkylthioxy,

(5) C_1-C_6 alkylacylamino,

(6) C_1-C_6 alkylacyloxy,

(7) amido

(8) C_1-C_6 alkylamino

(9) phenylamino,

(10) carbamyl

(11) carboxyl

(12) carboxy(C_2-C_5)alkoxy,

(13) carboxy(C_2-C5)alkylthioxy,

(14) heterocyclylacyl,

(15) heteroarylacyl,

(16) amino unsubstituted or substituted with C_1-C_6 alkyl,

(17) hydroxyl, or

(18) carboxyl methyl ester;

(II)-$(CH_2)_{0-3}$-J-[(-$(CH_2)_{0-3}$-K]$_{1-3}$ where K is as defined above and J is:

(A) a 5 to 7 atom monocyclic aryl group,

(B) a 8 to 12 atom multicyclic aryl group,

(C) a 5 to 7 atom heterocyclic_group,

(D) a 8 to 12 atom multicyclic heterocyclic group, or

(E) a 5 to 10 atom monocyclic or multicyclic cycloalkyl group;

(III) -$(CH_2)_{0-3}$-(C_3-C_7) cycloalkyl where cycloalkyl can be unsubstituted or substituted with one, two or three

(A) C_1-C_3 alkyl unsubstituted or substituted with 1, 2, 3, or 4 –F, -Cl, -Br, or -I,

(B) -CO-OH,

(C) -CO-O-(C_1-C_4 alkyl),

(D) -OH, or

(E) C_1-C_6 alkoxy,

(IV) -$(CH_2)_{2-6}$-OH,

(V) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are –H, C_1-C_4 alkyl and ϕ- and R_{C-aryl} is the same as R_{N-aryl},

(VI) -$(CH_2)_{0-4}$-$R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyl,

(O) phthalazinyl,

(P) isoxazolyl,

(Q) pyrazolyl,

(R) indolizinyl,

(S) indazolyl,

(T) benzothiazolyl,

(U) benzimidazolyl,

(V) benzofuranyl,

(W) furanyl,

(X) thienyl,

(Y) pyrrolyl,

(Z) oxadiazolyl,

(AA) thiadiazolyl,

(BB) triazolyl,

(CC) tetrazolyl,

(DD) 1, 4-benzodioxan

(EE) purinyl,

(FF) oxazolopyridinyl,

(GG) imidazopyridinyl,

(HH) isothiazolyl,

(II) naphthyridinyl,

(JJ) cinnolinyl,

(KK) carbazolyl,

(LL) β-carbolinyl,

(MM) isochromanyl,

(NN) chromanyl,

(OO) furazanyl,

(PP) tetrahydroisoquinoline,

(QQ) isoindolinyl,

(RR) isobenzotetrahydrofuranyl,

(SS) isobenzotetrahydrothienyl,

(TT) isobenzothiophenyl,

(UU) benzoxazolyl, or

(VV) pyridopyridinyl,

(VII) -$(CH_2)_{0\text{-}4}$-$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is the same as $R_{1\text{-heterocycle}}$,

(VIII) -$C(R_{C-1})(R_{C-2})$-CO-NH-R_{C-3} where R_{C-1} and R_{C-2} are the same or different and are:

(A) -H,

(B) -C_1-C_6 alkyl,

(C) -(C_1-C_4 alkyl)-$R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above for

$R_{1\text{-aryl}}$,

(D) -(C_1-C_4 alkyl)-$R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) -(C_1-C_4 alkyl)-$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) –$R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(G) –$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(H) –$(CH_2)_{1\text{-}4}$-OH,

(I) -$(CH_2)_{1\text{-}4}$-$R_{C\text{-}4}$-$(CH_2)_{1\text{-}4}$-$R_{C'\text{-aryl}}$ where $R_{C\text{-}4}$ is –O-, -S-, -NH- or –$NHR_{C\text{-}5}$- where $R_{C\text{-}5}$ is C_1-C_6 alkyl, and where $R_{C'\text{-aryl}}$ is as defined above,

(J) -$(CH_2)_{1\text{-}4}$-$R_{C\text{-}4}$-$(CH_2)_{1\text{-}4}$-$R_{C\text{-heteroaryl}}$ where $R_{C\text{-}4}$ and $R_{C\text{-heteroaryl}}$ are as defined above, or

(K) –$R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

and where $R_{C\text{-}3}$ is:

(A) -H,

(B) -C_1-C_6 alkyl,

(C) –$R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(D) –$R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,

(E) –$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(F) -(C_1-C_4 alkyl)-$R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(G) -(C_1-C_4 alkyl)-$R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above, or

(H) -(C_1-C_4 alkyl)-$R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,

(IX) -CH(ϕ)$_2$,

(X) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one, two or three:

(A) C_1-C_3 alkyl,

(B) –CF_3,

(C) -F, Cl, -Br and –I,

(D) C_1-C_3 alkoxy,

(E) $-OCF_3$,

(F) $-NH_2$,

(G) -OH, or

(H) $-C \equiv N$,

(XI) $-CH_2-C \equiv CH$;

(XII) $-(CH_2)_{0-1}-CHR_{C-5}-(CH_2)_{0-1}-\phi$ where R_{C-5} is:

(A) –OH, or

(B)$-CH_2-OH$;

(XIII) $-CH(-\phi)-CO-O(C_1-C_3$ alkyl);

(XIV) $-CH(-CH_2-OH)-CH(-OH)-\phi-NO_2$;

(XV) $-(CH_2)_2-O-(CH_2)_2-OH$;

(XVI) $-CH_2-NH-CH_2-CH(-O-CH_2-CH_3)_2$;

(XVII) $-(C_2-C_8)$ alkynyl; or

(XVIII) –H.

Typically, R_C is:

(I)-C_1-C_8 alkyl,

(II) $-(CH_2)_{0-3}-(C_3-C_7)$ cycloalkyl,

(III) $-(CH_2)_{0-3}-OH$,

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C\text{-aryl}}$,

(V) $-(CH_2)_{0-4}-R_{C\text{-heteroaryl}}$,

(VI) $-(CH_2)_{0-4}-R_{C\text{-heterocycle}}$,

(VII) $-C(R_{C-1})(R_{C-2})-CO-NH-R_{C-3}$,

(IX) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one or two:

(A) C_1-C_3 alkyl,

(B) $-CF_3$,

(C) -F, Cl, -Br or –I,

(D) C_1-C_3 alkoxy,

(E) $-OCF_3$, or

(XVI) –H.

It is preferred that R_C is:

(II) $-(CH_2)_{0-3}-(C_3-C_7)$ cycloalkyl,

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C\text{-aryl}}$,

(V) $-(CH_2)_{0-4}-R_{C\text{-heteroaryl}}$,

(VI) $-(CH_2)_{0-4}-R_{C\text{-heterocycle}}$,

(VII) $-C(R_{C-1})(R_{C-2})$-CO-NH-R_{C-3}, or

(IX) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring.

It is more preferred that R_C is:

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C\text{-aryl}}$,

(V) $-(CH_2)_{0-4}-R_{C\text{-heteroaryl}}$,

(VI) $-(CH_2)_{0-4}-R_{C\text{-heterocycle}}$, or

(IX) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring.

It is most preferred that R_C is:

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C\text{-aryl}}$ where $R_{C\text{-aryl}}$ is phenyl,

(V) $-CH_2-R_{C\text{-heteroaryl}}$,

(VI) $-CH_2-R_{C\text{-heterocycle}}$, or

(IX) -cyclohexyl ring fused to a phenyl ring. Further, it is preferred that when R_C is phenyl, it is substituted in the 3-position or 3,5-positions.

Suitable reaction conditions for opening the lactone (XI) to produce the desired hydroxyethylene end product (XII) include those of the $AlMe_3$-mediated coupling reaction disclosed in the literature procedure of S.F. Martin et al., *Tetrahedron Lett.* 1998, 39, 1517-1520. When the substituted C-terminal amine is a 1-amino-3,5-cis-dimethyl cyclohexyldicarboxylate it is preferrably prepared as follows. To dimethyl-5-isophthalate in acetic acid and methanol, is added rhodium in alumina in a high-pressure bottle. The bottle is saturated with hydrogen at 55 psi and shaken for one week of time. The mixture is then filtered through a thick layer of celite cake and rinsed with methanol three times, the solvents are removed under reduced pressure (with heat) to give a concentrate. The concentrate is triturated with ether and filtered again to give the desired C-terminal amine. When the substituted C-terminal amine is 1-amino-3,5-cis-dimethoxy cyclohexane it is preferably following the general procedure above and making non-

critical variations but starting wth 3,5-dimethoxyaniline. When the substituted C-terminal amine is an aminomethyl group where the substituent on the methyl group is an aryl group, for example NH_2-CH_2-$R_{C\text{-aryl}}$, and NH_2-CH_2-$R_{C\text{-aryl}}$ is not commercially available it is preferrably prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substitutent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 313. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by hydrogen/catalyst to give the C-terminal amine of formula NH_2-CH_2-$R_{C\text{-aryl}}$.

CHART B, as defined within, sets forth a process for production of the amide (VII). Preparation of the amide (VIII) starts with the reaction of an appropriate amino-indanol (XIV) with an appropriate haloketone (XII) to afford the hydroxy indane (XV). The amino-indanol (XIV) and haloketone (XII) are well known to those skilled in the art or can be readily prepared from known compounds by methods well known to those skilled in the art. The X substituent of the haloketone is typically F, Cl, Br, or I. Preferably X is Cl. For the amino haloketone (XII), R_2 is:

(I) -H,

(II) C_1-C_6 alkyl, or

(III) -$(CH_2)_{0\text{-}4}$-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is (C_3-C_6)cycloalkyl, $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$ where $R_{1\text{-aryl}}$ and $R_{1\text{-heteroaryl}}$ are as defined above,

Certain hydroxyethylene compounds of formula (XII) contain acidic functionality capable of forming base addition salts. Additionally, certain hydroxyethylene compounds of formula (XII) contain basic functionality capable of forming acid addition salts. For example, certain hydroxyethylene compounds of formula (XII) are amines and as such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding hydroxyethylene compounds of formula (XII) since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undersirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically

acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids: hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, methanesulfonic, CH_3-$(CH_2)_{n1}$-COOH where n_1 is 0 thru 4, HOOC-$(CH_2)n_1$-COOH where n is as defined above, HOOC-CH=CH-COOH, and φ-COOH. Additionally, preferred pharmaceutically acceptable salts include salts of the following bases: triethanolamine, N-methylglucamine, diethanolamine, ethanolamine, tris(hydroxymethyl)aminomethane (TRIS), ammonia, and carbonate, bicarbonate, phosphonate, or hydroxide salts of an alkali or alkaline earth metal. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986).

Preferred hydroxyethylene compounds of formula (XII), include, for example,
N-[(1*S*, 2*S*, 4*R*)-1-(3,5-Difluorobenzyl)-4-(*syn*, *syn*)-(3,5 dimethoxycyclohexylcarbamoyl)-2-hydroxyhexyl]-*N,N*-dipropylisophathalamide,
6-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-hexanoic acid,
5-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-pentanoic acid,
4-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-butyric acid,
3-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-propionic acid,
8-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-octanoic acid,
8-[6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-octanoic acid methyl ester,
N-[4-(*R*)-Butylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(R)-isobutylcarbamoyl-hexyl]-*N,N*-dipropyl-isophthalamide,
N-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

N-[4-(*R*)-(Cyclohexylmethyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(piperidine-1-carbonyl)-hexyl]-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(2-dimethylamino-ethylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

N-[4-(*R*)-(Butyl-methyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(3-hydroxy-propylcarbamoyl)-hexyl]-*N,N*-dipropyl-isophthalamide,

4-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(3-dimethylamino-propylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-methyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-propyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxyl-2-(*R*)-isobutyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([2-(*R*)-Benzyl-6-(3,5-difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(S)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(S)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(2-morpholin-4-yl-ethylcarbamoyl)-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-isobutylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[4-(*R*)-(2-Diethylamino-ethylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-pentyl)-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[4-(*R*)-(Adamantan-2-ylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-methyl-5-morpholin-4-yl-5-oxo-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

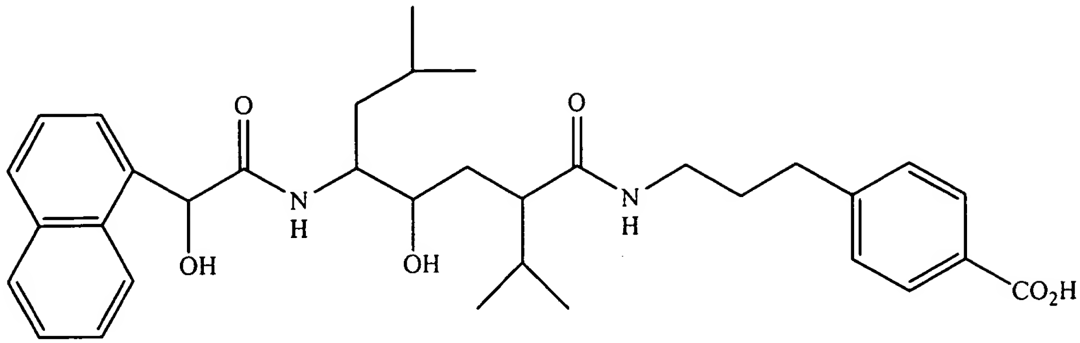
N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(4-fluoro-benzylcarbamoyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-phenethylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-[(furan-2-ylmethyl)-carbamoyl]-2-(S)-hydroxy-pentyl)-5-methyl-*N,N*-dipropyl-isophthalamide, or

N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(prop-2-ynylcarbamoyl)-pentyl]-5-methy-*N,N*-dipropyl-isophthalamide.

Additional preferred hydroxyethylene compounds of formula (XII) include, for example those of the following formulae:



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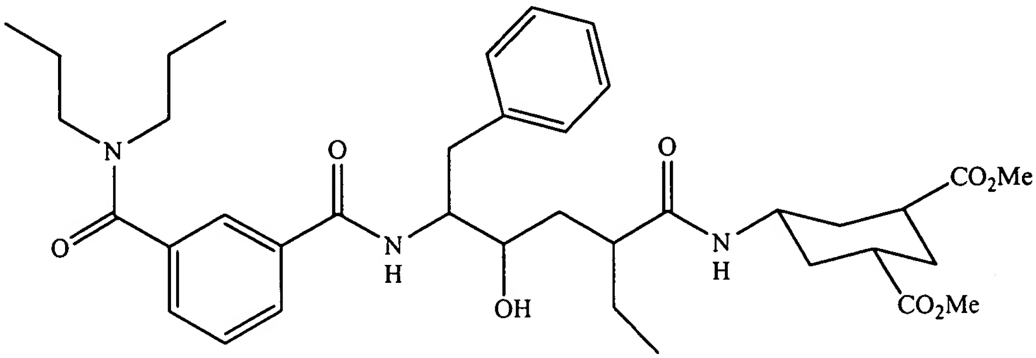

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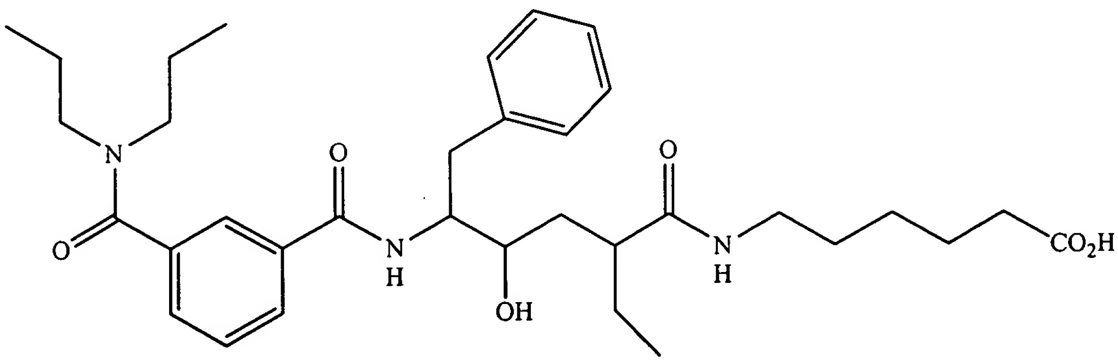

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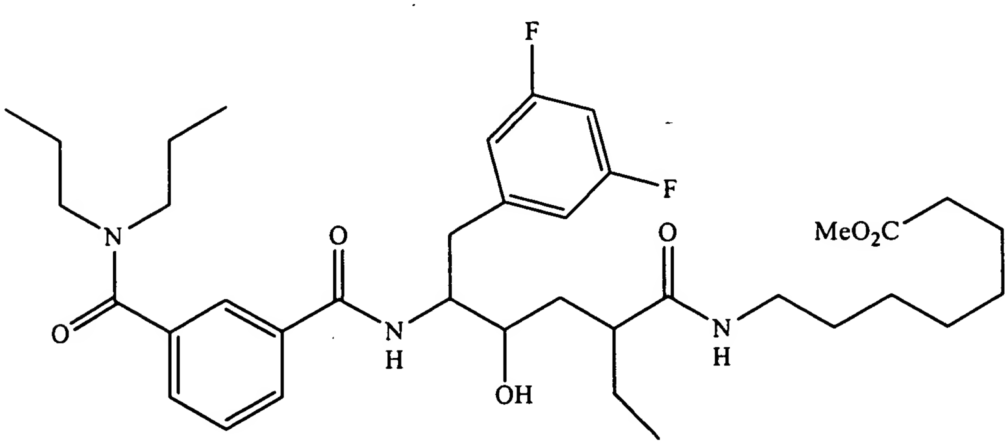

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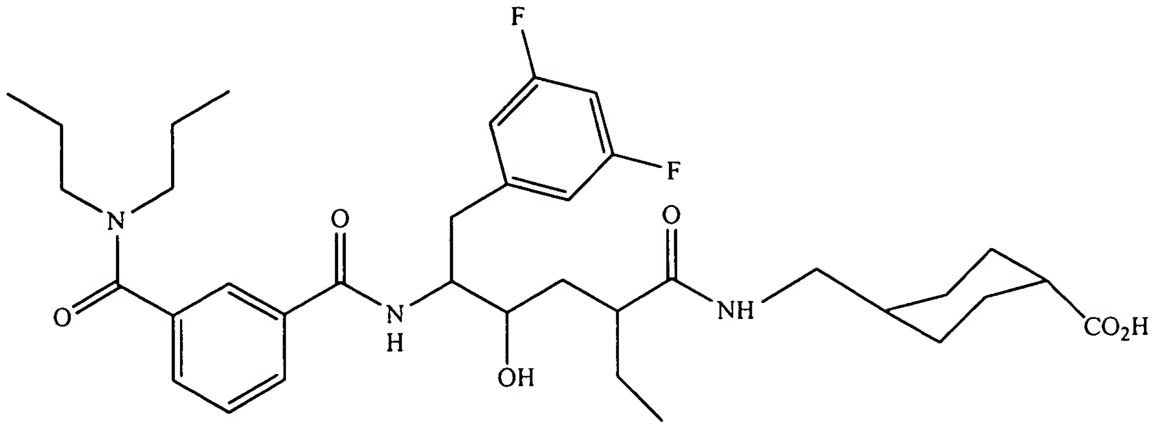

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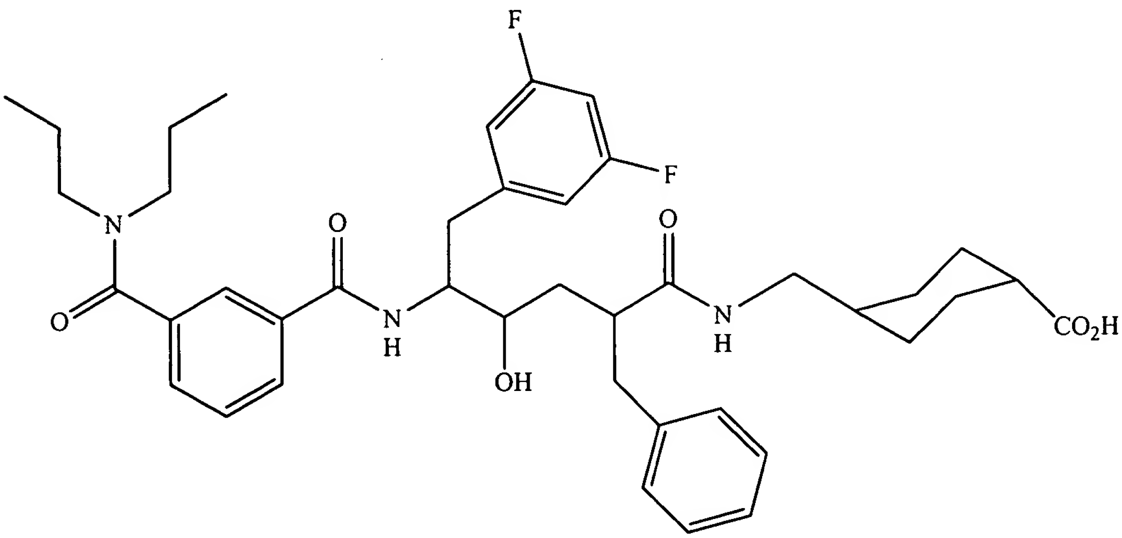

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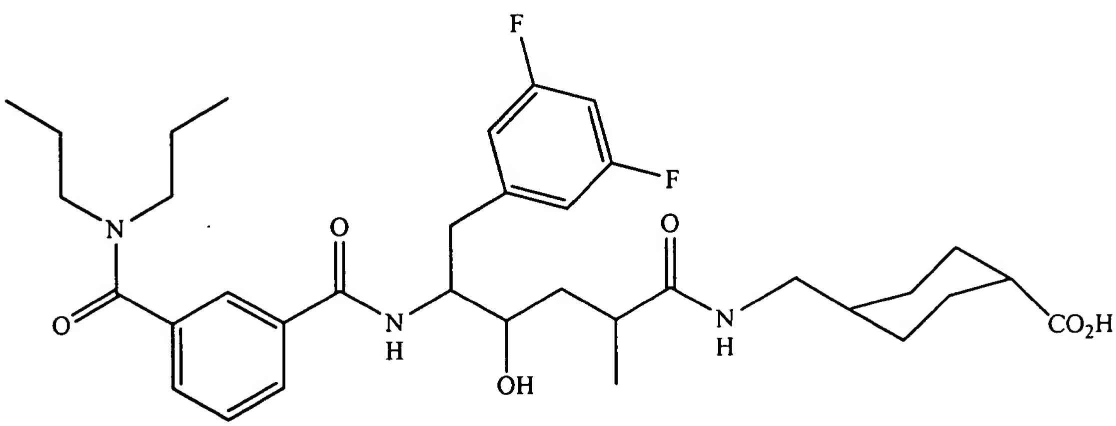

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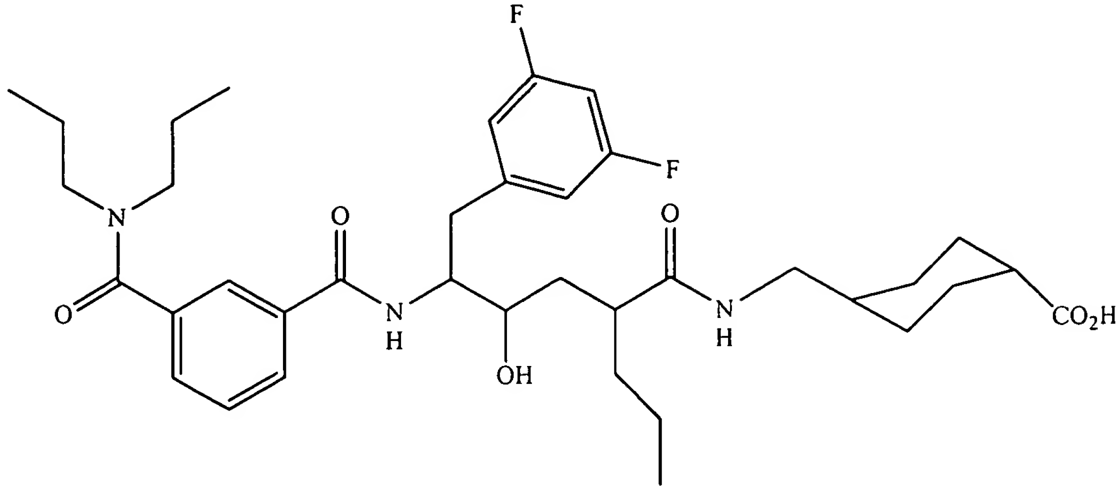


Most preferred hydroxyethylene compounds of formula (XII), include, for example, 4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-propyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid.

6-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-hexanoic acid,
8-[6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-octanoic acid methyl ester,
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid
4-(*anti*)-([2-(*R*)-Benzyl-6-(3,5-difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid, and
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-methyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid.

The hydroxyethylene compounds of formula (XII), and pharmaceutically acceptable salts thereof, are useful for treating humans suffering from Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing

its potential consequences, i.e. single and recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration , diffuse Lewy body type Alzheimer's disease. It is preferred the the disease is Alzheimer's disease.

When treating these diseases, the hydroxyethylene compounds of formula (XII) can either be used individually or in combination as is best for the patient.

With regard to these diseases the term "treating" means that the hydroxyethylene compounds of formula (XII) can be used in humans with existing disease. The hydroxyethylene compounds of formula (XII) will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that if the compounds of the present invention are administered to those who do not now have the disease but who would normally get the disease or be at increased risk for the disease, they will not get the disease. In addition, "preventing" also includes delaying the development of the disease in an individual who will ultimately get the disease or would be at risk for the disease. By delaying the onset of the disease, the hydroxyethylene compounds of formula (XII) have prevented the individual from getting the disease during the period in which the individual would normally have gotten the disease or reduce the rate of development of the disease or some of its effects but for the administration of the hydroxyethylene compounds of formula (XII) up to the time the individual ultimately gets the disease. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to familial history and/or due to the presence of one or more biological markers for the disease such as a known genetic mutation of APP or by analysis of APP cleavage products in body tissues or fluids.

In treating or preventing the above diseases the hydroxyethylene compounds of formula (XII) are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration as is known to those skilled in the art.

In treating a patient with any of the diagnosed above conditions a physician may administer hydroxyethylenes of formula (XII) immediately and continue indefinitely.

In treating patients who do not at the present have Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be diagnosed with Alzheimer's through the detection of the genetic marker APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, the administration of the hydroxyethylene compounds of formula (XII) may be started before they appear and treatment continued indefinitely to prevent or delay the outset of the disease.

The hydroxyethylene compounds of formula (XII) can be administered orally, parenterally (IV, IM, depo-IM, SQ and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically and rectally. The invention here is the novel hydroxyethylene compounds of formula (XII). Dosage forms known to those skilled in the art are suitable for delivery of the novel hydroxyethylene compounds of formula (XII).

Hydroxyethylene compounds of formula (XII) may be administered enterally or parenterally. When administered orally, hydroxyethylene compounds of formula (XII) can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the hydroxyethylene compounds of formula (XII) need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the hydroxyethylene compounds of formula (XII) be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the hydroxyethylene compounds of formula (XII) be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the hydroxyethylene compounds of formula (XII) from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also

well known to those skilled in the art. When administered orally the therapeutically effective amount is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

Hydroxyethylene compounds of formula (XII) may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described in US 5,145,684. And nano crystalline dispersions of, for example, HIV protease inhibitors and their method of use are described in US 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

In addition, the hydroxyethylene compounds of formula (XII) can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SC or depo-SC. When administered parenterally, the hydroxyethylene compounds of formula (XII) should deliver a therapeutically effective amount about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily. When a depo formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day or on a monthly amount the dose for one month should be from about 15 mg to about 1,500 mg. Because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo-IM injection.

The hydroxyethylene compounds of formula (XII) can be given sublingually. When given sublingually, the hydroxyethylene compounds of formula (XII) should be given one thru four times daily in the same amount as for IM administration.

The hydroxyethylene compounds of formula (XII) can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the hydroxyethylene compounds of formula (XII) for intranasal administration is the same as for IM administration.

The hydroxyethylene compounds of formula (XII) can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the

hydroxyethylene compounds of formula (XII) for intrathecal administration is the same as for IM administration.

The hydroxyethylene compounds of formula (XII) can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the hydroxyethylene compounds of formula (XII) needed to administered the patch is preferred. Further, two or more patches may be needed. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the hydroxyethylene compounds of formula (XII) be delivered as is known to those skilled in the art. The hydroxyethylene compounds of formula (XII) can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about 500 mg.

The hydroxyethylene compounds of formula (XII) can be administered by implants as is known to those skilled in the art. When administering a hydroxyethylene compound of formula (XII) by implant, the therapeutically effective amount is the same as for depot administration.

Again, the invention here is a new method of using hydroxyethylene compounds of formula (XII) and hydroxyethylene compounds of formula (XII). Given a particular hydroxyethylene compound of formula (XII), and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the hydroxyethylene compounds of formula (XII).

The hydroxyethylene compounds of formula (XII) are used in the same manner by the same routes of administration using the same pharmaceutical dosage forms and at the same dosing schedule for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including

dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration , diffuse Lewy body type of Alzheimer's disease. The hydroxyethylene compounds of formula (XII) can be used with each other or with other agents used to treat or prevent the conditions listed above. Such agents include gamma-secretase inhibitors, anti-amyloid vaccines and pharmaceutical agents such as donepezil hydrochloride (ARICEPT™ Tablets), tacrine hydrochloride (COGNEX™ Capsules) or other acetylcholine esterase inhibitors and with direct or indirect neurotropic agents of the future.

Inhibition of APP Cleavage

The compounds of the invention inhibit cleavage of APP at the β-secretase cleavage site, Met595-Asp596 for the APP695 isoform. While not wishing to be bound by a particular theory, inhibition of β-secretase acitivity is thought to inhibit production of beta amyloid beta peptide (Aβ). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a β-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the β-secretase cleavage site. Reduction of APP cleavage at the β-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patent No. 5,942,400.

The enzymatic activity of β-secretase and the production of Aβ can be analyzed *in vitro* or *in vivo,* using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of β-secretase cleavage product produced in comparison to a control, where

β-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

β-secretase

Various forms of β-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human ASP2a and Asp2b has been characterized, for example, in published PCT patent applications WO98/22597 and WO00/17369, as well as synthetic forms of the enzyme.

The comounds of the invention inhibit 50% of the β-secretase enzymatic acitivity at a concentration of from about 0.1nM to about 200 μM, preferably at a concentration of from about 10nM to about 100μM, more preferably from about 100 nM to about 50 μM, and most preferably from about 1μM to about 10μM.

APP substrate

Assays that demonstrate inhibition of β-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, Nature 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, Nature 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the β-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400.

The APP substrate may also be a fusion peptide, formed of a peptide having the β-secretase cleavage site fused to a peptide that confers a characteristic useful for enzymatic assay, for example, isolation and/or detection properties.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of β-secretase results in cleavage of the substrate at the β-secretase

cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

Cellular assay

Cells expressing an APP substrate and an active β-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of β-secretase can be measured by analysis of one or more APP cleavage products. For example, cellular inhibition of β-secretase activity would be expected to decrease release of the cleavage product, Aβ.

Human cell lines that normally process Aβ from APP provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of Aβ and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immoassay (EIA or ELISA).

Primary neuronal cell cultures from human brain or from brain tissue obtained from transgenic animals expressing APP, particurly human APP, and capable of processing APP to detectable Aβ are also useful cells for assay of β-secretase cleavage activity. For example, primary human neuronal cell cultures derived from human embryonic tissues express endogenous β-secretase and endogenous APP. Enzymatic activity is assayed in the presence of the inhibitory compound, and cleavage products, such as Aβ, are measured. Another useful primary cell culture system employs cells derived from brain tissue of transgenic mice, for example, from PD-APP mice expressing a transgenic APP having a mutation at V717 or the Swedish mutation.

Although both neural and non-neural cells process and release Aβ, levels of endogenous β-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced β-secretase activity, enhanced processing of APP to Aβ, and/or enhanced production of Aβ are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced β-secretase activity and producing amounts of Aβ that can be readily measured.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect Aβ include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the Aβ peptide; antibodies 162 and 164 (New York State Insititute for Basic Research, Staten Island, NY) that are specific for hAβ 1-40 and 1-42, respectively. Another useful antibody is SW192, as discussed above, that recognizes an epitope uncovered on the C-termial cleavage fragment following APP-SW cleavage mediated by β-secretase.

Animal Models

Animal models useful in testing the compounds of the invention include those expressing elevated levels of Aβ, demonstrating an enhanced amount of Aβ deposits, and/or increased number or size of beta amyloid plaques as compared with control animals. Such animal models include transgenic mammals. Suitable transgenic animals include rodents transformed with a variant or modified APP that results in a measured amount Aβ in the animal that is greater than that produced in a non-transformed control. Examples of suitable transgenic animal models include a mouse transformed with APP-SW, described, for example, in U.S. Patent No. 5,877,399, 5,612,486, and 5,850,003. Other suitable animals are transformed with V717 APP, as described, for example, in U.S. Patent No. 5,877,015, and in Ganes et.al., 1995, *Nature* 373:523.

Cleavage of APP at the β-secretase cleavage site can be analyzed in these animals by measure of cleavage fragments in the animal's brain tissues, and possibly cerebral fluids, as well as by analysis of beta amyloid plaques and assessment of necrosis in the animal's brain tissues.

On contacting an APP substrate with a β-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of Aβ from the substrate, the of the invention are effective to reduce β-secretase-mediated cleavage of APP at the β-secretase cleavage

site and/or effective to reduce released amounts of Aβ. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce Aβ deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of Aβ, to slow the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Assay Systems

Assays for determining APP cleavage at the β-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

Cell free assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369 and U.S. Patent No. 5,942,400. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a β-secretase and an APP substrate having a β-secretase cleavage site.

An APP substrate containing the β-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of a β-secretase enzyme, for example human (h) Asp2a, hAsp2b, a fragment thereof, or a synthetic or recombinant polypeptide variant of hAsp2a or hAsp2b having β-secretase activity and effective to cleave the β-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its β-secretase cleavage products. Useful modifications include the insertion of a

known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200nM-10μM substrate, approximately 10-200 pM enzyme, and approximately 0.1nM-10μM inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37^{O}C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific β-enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

cellular assays

Numerous cell-based assays to analyze β-secretase activity and/or processing of APP to release Aβ. In one embodiment, cells that naturally express β-secretase are used. Alternatively, cells are modified to express a recombinant β-secretase, for example, hAsp2a, hAsp2b, or a recombinant or synthetic variant enzyme as discussed above.

The APP substrate may be added to the culture medium or expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the β-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed..

Contact of an APP substrate with a β-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate the inhibitory activity. β-secretase activity or function, for example, as measured by cleavage of the APP substrate and detection of fragments and/or markers, can take numerous forms, as discussed above for non-cellular assays. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at

least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In such assays, for example, the cells expressing APP and β-secretase are incubated in a culture medium under conditions to permit processing of the APP by the enzyme and release of Aβ into the medium and accumulation of other fragments of APP in cell lysates. The inhibitory activity of the compounds of the invention can be demonstrated by incubating the cells in the presence and absence of the compound. On exposure of the cells to the compound inhibitor, the amount of Aβ released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of β-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells, where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW. In the cellular assay, cells are incubated in the presence or absence of the inhbitor, under conditions suitable for β-secretase enzymatic activity at it's cleavage site on the APP substrate. Cell supernatant is harvested, and analyzed for cleavage fragments, for example using immunoassay.

In vivo assays: animal models

Various animal models can be used to analyze β-secretase activity and/or processing of APP to release Aβ, as described above. For example, transgenic animals expressing APP substrate and β-secretase enzyme can be used to demonstrate inhibitory activity of the comounds of the invention. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Certain transgenic animal models for AD have been described, for example, in U.S. Patents No: 5,877,399, 5,612,486, 5,387,742, 5,720,936, and 5,811,633.

Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compound inhibitors. Administration of the compound inhibitor in a pharmaceutally effective carrier and via an administrative route that reaches the target

tissue in an appropriate therapeutic amount is preferred. Inhibition of β-secretase-mediated cleavage of APP and of Aβ release can be measured by analysis of the cleavage products in the body fluids or tissues of the animal. Analysis of brain tissues for Aβ deposits or plaques is also made.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular hydroxyethylene compounds of formula (XII) administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula CH_3-C(=Z_1)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)H_2. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left

which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R_6" represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X_1)(X_2)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (ß) configuration and is indicated by an unbroken line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as -C(=R_i)- might be bivalent and be defined as oxo or keto (thus forming

a carbonyl group (-CO-) or as two separately attached monovalent variable substituents α-R_{i-j} and β-R_{i-k}. When a bivalent variable, R_i, is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form "α-R_{i-j}:β-R_{i-k}" or some variant thereof. In such a case both α-R_{i-j} and β-R_{i-k} are attached to the carbon atom to give -C(α-R_{i-j})(β-R_{i-k})-. For example, when the bivalent variable R_6, -C(=R_6)- is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are α-R_{6-1}:β-R_{6-2}, ... α-R_{6-9}:β-R_{6-10}, etc, giving -C(α-R_{6-1})(β-R_{6-2})-, ... -C(α-R_{6-9})(β-R_{6-10})-, etc. Likewise, for the bivalent variable R_{11}, -C(=R_{11})-, two monovalent variable substituents are α-R_{11-1}:β-R_{11-2}. For a ring substituent for which separate α and β orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and β designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula -C_1(R_i)H-C_2(R_j)H- (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group -X-Y-, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form -CH_2-CH_2-O-CO- ..." means a lactone in which the carbonyl is bonded to C_2. However, when designated "... R_j and R_i are taken together to form -CO-O-CH_2-CH_2-the convention means a lactone in which the carbonyl is bonded to C_1.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C_1-C_4", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined.

Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-$(CH_2)_n$-0-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

It is to be understood that the recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

It is to be understood that all numbers and fractions thereof are presumed to be modified by the term "about."

It is to be understood that "a" as used herein includes both the singular and plural.

The general definitions used herein have the following meanings within the scope of the present invention.

II. DEFINITIONS

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

psi refers to pounds/in^2.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or *t*-butoxycarbonyl, $-CO-O-C(CH_3)_3$.

CBZ refers to benzyloxycarbonyl, $-CO-O-CH_2-\varphi$.

TFA refers to trifluoracetic acid, CF_3-COOH.

CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from TMS.

$-\phi$ refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit. MH^+ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

"APP", amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example as disclosed in U.S. Patent No. 5,766,846.

"Aβ", beta amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

"β-secretase" is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of Aβ. Human β-secretase is described, for example, in WO00/17369.

A compound of the invention is any compound described herein having inhibitory activity against a β-secretase enzyme; against the production of Aβ; against the production of beta amyloid deposits or plaques; or against the development or

progression of neurodegenerative disease such as AD, measured, for example, by one or more of the assays described herein.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

TBDMSCl refers to *t*-butyldimethylsilyl chloride.

TBDMSOTf refers to *t*-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

Ac= acetyl (methylcarbonyl)
aq. = aqueous
bd = broad doublet
bs = broad singlet
c = concentration (g/mL)
cc = cubic centimeter
d = doublet
DCM = dichloromethane = methylene chloride = CH_2Cl_2
de = diastereomeric excess
EDTA = ethylene diamine tetraacetic acid
eq. = equivalents
EtOAc = ethyl acetate
EtOH = ethanol
g = grams
HOBT = 1-hydroxybenzotriazole
h = hour
IC_{50} = inhibitory concentration of a compound that reduces enzyme activity by half.
iso = an alkyl chain having the ending group 2-methylpropyl, i.e. $-CH(CH_3)_2$.
IM= intramuscularly
IV= intravenously
SC= subcutaneously
L = liter
LDA = lithium diisopropyl amide
m = multiplet
max = maximum
mg = milligram

mL = milliliter
mm = millimeter
mM = millimolar
mmol = millimole
mp = melting point
MeOH = methanol
meq = milliequivalent
MsOH = methanesulfonic acid
n = normal, i.e. unbranched, e.g. *n*-Pr is $-CH_2-CH_2-CH_3$
N = normal
ng = nanogram
nm = nanometers
OD = optical density
PEPC = 1 -(3-(1 -pyrrolidinyl)propyl)-3-ethylcarbodiimide
pg = picogram
pM = picoMolar
R_f = ratio of movement of a substance on a thin layer chromatogram in comparison to the movement of the solvent front.
δ = units of measurement in nuclear magnetic resonance spectroscopy which are relative to a standard, e.g. tetramethyl silane.
q = quartet
quint. = quintet
rpm = rotations per minute
s = singlet
t = triplet
t or *tert* = tertiary in an alkyl chain, e.g. *t*-butyl is $-C(CH_3)_3$.
μL = microliter
μM = micromolar (an expression of concentration in micromoles/ liter)
s = singlet
t = triplet
UV = ultraviolet

Unless otherwise indicated, all functional group radicals (e.g., alkyl, aryl, cycloalkyl, cyclic heteroaryl, heterocycle, etc.) can be substituted or unsubstituted. Substituted functional group radicals can be substituted with one or more substituents, unless indicated otherwise. Suitable substituents for substituted functional group radicals generally include halogen, hydroxy, alkoxy, alkyl, aryl, arylalkyl, alkylaryl, arylalkoxy, and the like. It will be understood that the terminology "X radical substituted by a/an Y" includes the "X" radical being substituted by two or more "Y", unless indicated otherwise.

"Alkyl" refers to linear or branched, saturated aliphatic hydrocarbon radicals, such as, for example, methyl, ethyl, propyl, butyl, octyl, isopropyl, tert-butyl, sec-pentyl, and the like.

"Cycloalkyl" refers to cyclic aliphatic hydrocarbon radicals, such as, for example, 3- to 8-member hydrocarbon rings (e.g., cyclohexyl or cyclopentyl), bicyclic 4- to 10-member hydrocarbon ring systems, and a tricyclic 8- to 14-member hydrocarbon ring systems. Monocyclic cycloalkyl groups include, for example, cyclohexane and cyclopentane. Multicyclic cycloalkyl groups include cyclohexyl, cyclopentyl, and 1, 2, 3, 4-tetrahydrohaphthyl for example.

"Heterocycle" refers to cyclic, non-aromatic radicals containing at least two carbon atoms and 1 to 3 heteroatoms selected from O, N, and S as members of at least one ring. Examples of such radicals include 3- to 8-member rings; bicyclic 4- to 10-member ring systems, and tricyclic 8- to 14-member ring systems, where at least one ring (and in some instances each of the rings) of any of these examples contains 1 to 3 heteroatoms selected from O, N, and S as members of the ring. Monocyclic heterocyclic groups include morpholinyl, piperazinyl, and tetrahydrofuranyl, for example. Multicyclic heterocyclic groups include decahydroquinoline, cyclohexene oxide, and 3-amino-3-azabicyclo [3.3.0] octane, for example.

"Alkylene' refers to bivalent, linear or branched, saturated aliphatic hydrocarbon radicals, such as, for example, methylene, ethylene, propylene, butylene, octylene, isopropylene, tert-butylene, sec-pentylene, and the like.

"Alkenyl" refers to linear or branched aliphatic hydrocarbon radicals containing at least one double bond, such as, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methyl-1-propenyl, and the like.

"Alkynyl" refers to linear or branched aliphatic hydrocarbon radicals containing at least one triple bond, such as, for example, ethynyl (acetyl), 1-propynyl, 2-propynyl, 1-butynyl, and the like.

"Aryl" refers to cyclic aromatic hydrocarbon radicals having a single ring, such as phenyl, multiple rings, such as biphenyl, and multiple condensed rings, such as naphthyl and anthryl. Monocyclic aryl groups include phenyl, for example. Multicyclic aryl groups include naphthyl and anthryl, for example.

"Amine" includes primary, secondary and tertiary amines which may be in straight or branched chains or, in the case of secondary and tertiary amines within rings (e.g. morpholine and piperazine).

"Heteroaryl" refers to a cyclic aromatic rings having 1 to 4 hetero atoms selected from S, O, and N; and aromatic 7 to 10 membered organic stable bicyclic rings having 1 to 5 hetero atoms selected from S, O, and N. Examples of such radicals include 3- to 8-member rings; bicyclic 4- to 10-member ring systems; and tricyclic 8- to 14-member ring systems, where at least one ring (and in some instances each of the rings) of any of these examples contains 1 to 3 heteroatoms selected from O, N, and S as members of the ring.

"Acyloxy" refers to the groups R-C(O)O-, substituted R-C(O)O-, cycloalkyl-C(O)O-, aryl-C(O)O-, and heterocyclic-C(O)O where R = alkyl, and alkyl, cycloalkyl, aryl, and heterocyclic are as defined herein.

"Acylamino" refers to the groups R-C(O)N-, substituted R-C(O)N-, cycloalkyl-C(O)N-, aryl-C(O)N-, and heterocyclic-C(O)N- where R = alkyl, and alkyl, cycloalkyl, aryl, and heterocyclic are as defined herein.

"Amide" and "amido" refer to a functional group containing a carbon atom double-bonded to an oxygen atom and additionally singly bonded to a nitrogen atom [-C(O)-N]. "Primary" amide describes an unsubstituted amide group [-C(O)-NH_2]. "Secondary" and "tertiary" amides are amides in which nitrogen is substituted with one and two non-hydrogen groups respectively. The term "lactam" refers to a cyclized amide, i.e. a secondary or tertiary amide wherein the carbonyl carbon and the nitrogen atom are adjacent members of a ring.

"Halogen" refers to fluoro, chloro, bromo, and iodo radicals.

"Lactone" refers to cyclized ester of a carboxylic acid.

"Thio" refers to the replacement of oxygen by sulfur in a defined radical. Examples of thio compound include alkylthioxy compounds (e.g. alkyl-S-).

"Thioxyalkyl" refers to the divalent radical -S-alkyl-, where alkyl is as defined above. Examples of thioxyalkyl moietites include alkyl-S-alkyl moieties, such as CH_3-S-CH_2CH_2-.

"Alkoxy" refers to the radical -O-alkyl with alkyl as defined above. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy, and the like.

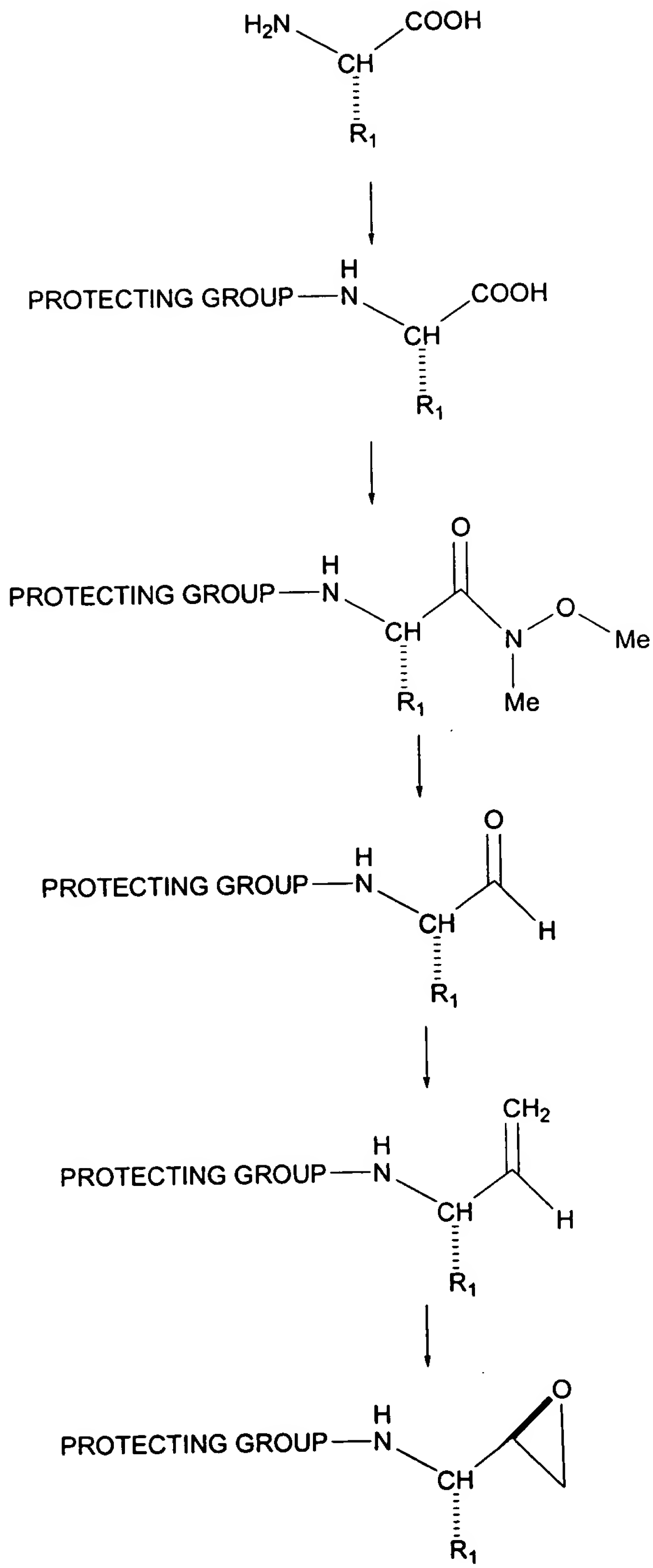
"Arylalkyl" and "aralkyl" refer to an alkyl radical substituted with an aryl.

"Alkylaryl" refers to an aryl radical substituted with an alkyl.

All the terms "carboxyl", "carboxylic acid", "carboxylate" and "carbamoyl" are terms referring to functional groups containing a carbon atom double-bonded to an oxygen atom [C=O, also called an acyl or a carbonyl group, represented in linear notation as –C(O)-] and additionally single- bonded to another oxygen atom [-C(O)-O-], and in the case of carbamoyl, additionally a nitrogen atom is also bonded to the carbonyl carbon to give -N-C(O)-O-. Carboxyl, carboxylate and carbamate include the corresponding pharmaceutically acceptable C_1 -C_6 alkyl and C_6-C_{10} aryl esters and secondary and tertiary amides.

Combinations of these terms for functional group radicals are also used. Typically, the last term in the designation contains the radical that bonds to the remainder of the chemical structure. For example, "haloalkyl" refers to an alkyl radical substituted by a halogen, "cycloalkylalkyl" refers to alkyl radical substituted by a cycloalkyl, and "alkylcycloalkyl" refers to a cycloalkyl radical substituted by an alkyl.

Chart A



(I)

(II)

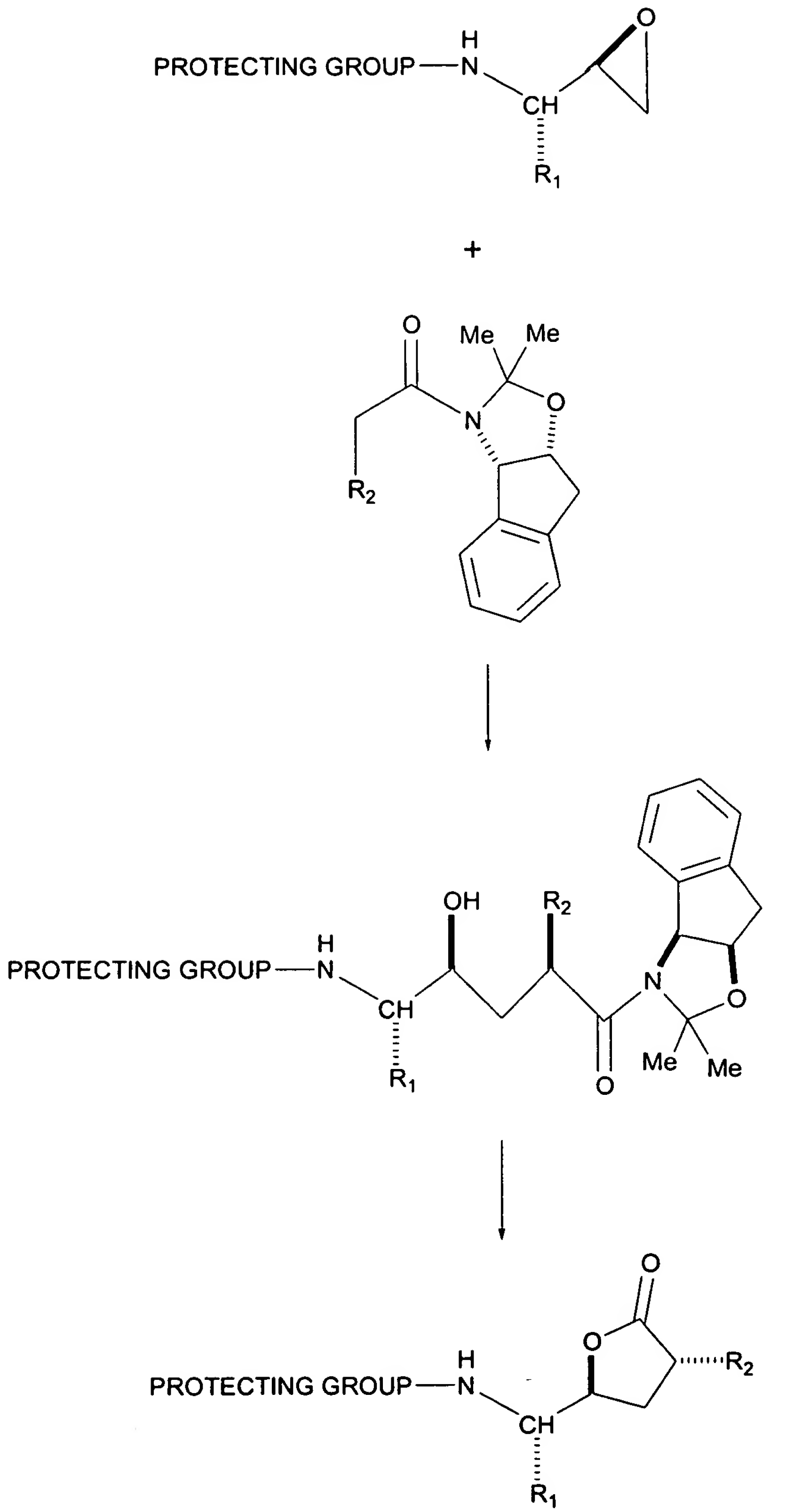
(III)

(IV)

(V)

(VI)

Chart A (continued)



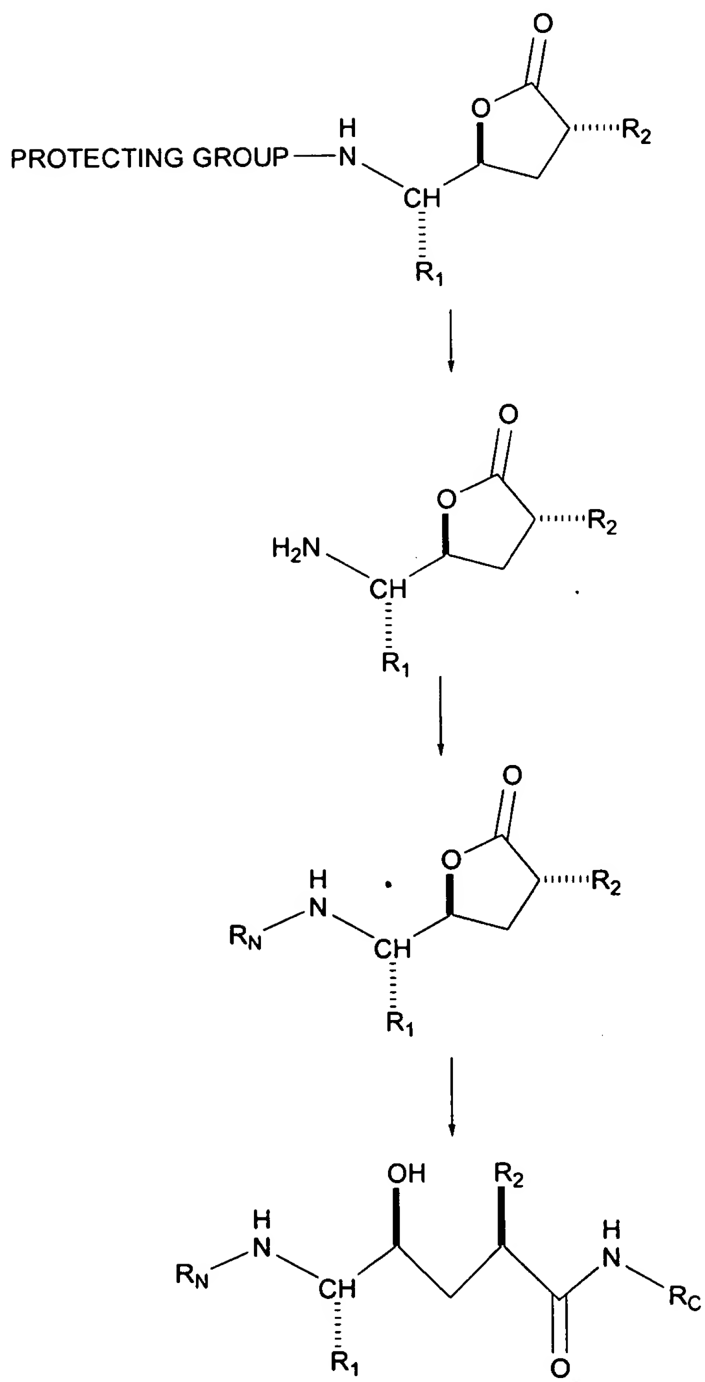
(VI)

(VII)

(VIII)

(IX)

Chart A (continued)



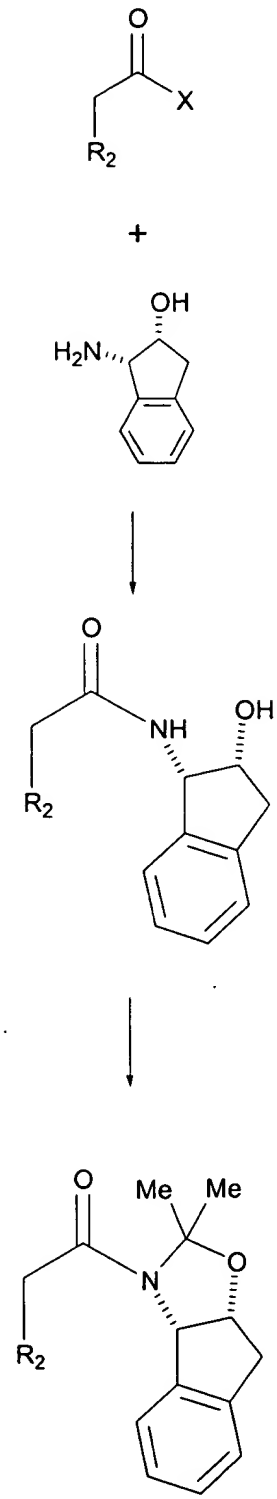
(IX)

(X)

(XI)

(XII)

Chart B



(XIII)

(XIV)

(XV)

(VII)

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

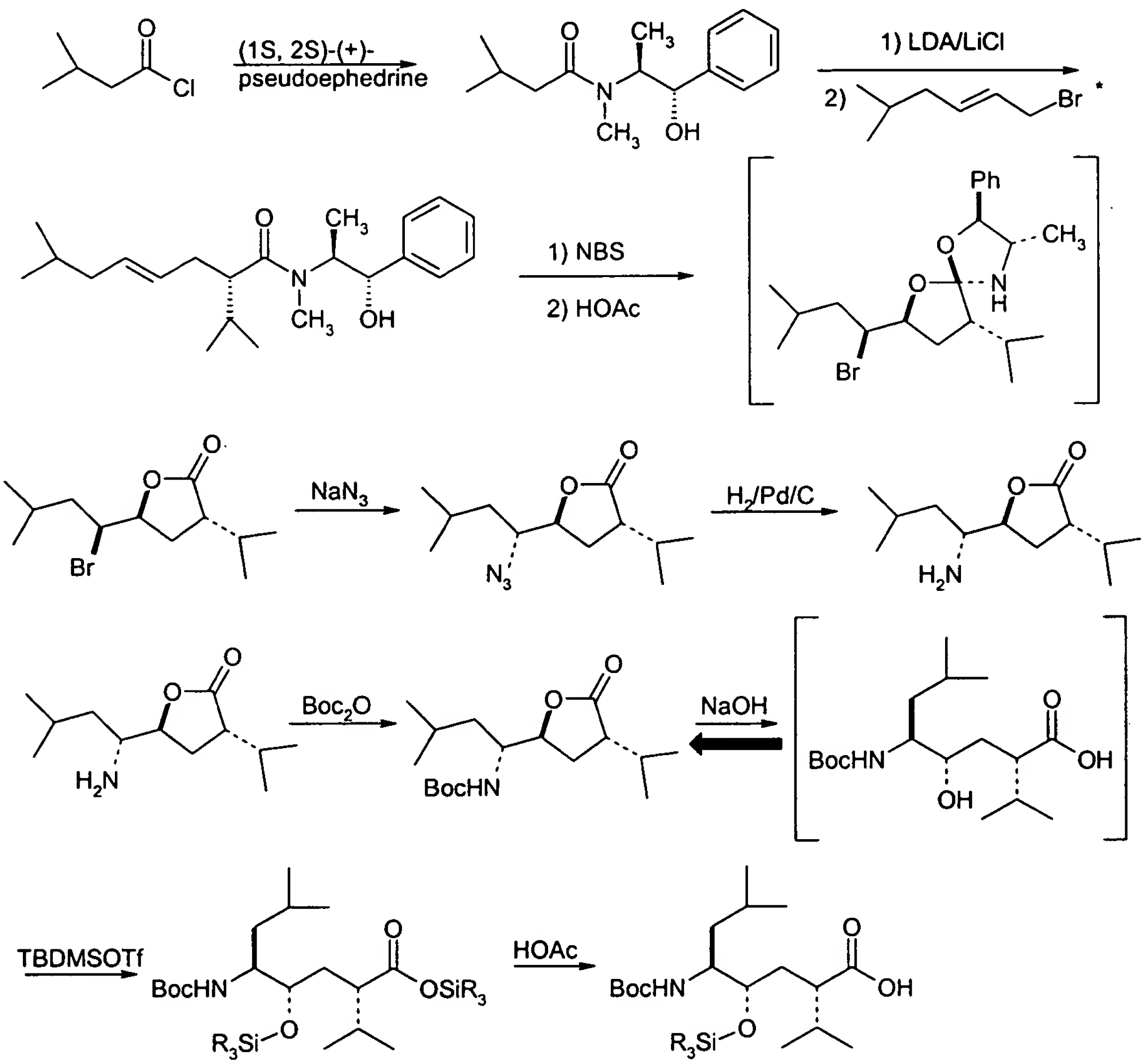
Preparations of the novel compounds of the present invention utilizing the hydroxyethylene isostere are illustrated in the following examples, which are not, however, intended to be any limitation thereof.

Methods of Synthesis

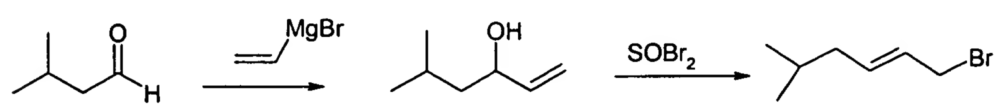
The following reaction schemes illustrate methods of construction of the hydroxyethylene dipeptide isosteres provided in examples 1-13. Variations of starting materials may be used in these reactions to prepare hydroxyethylene cores having other side chain groups. Substitutions of available starting materials to achieve the desired side chain variants will be apparent to one of ordinary skill in the art.

Scheme I

Synthesis of a protected hydroxyethylene moiety suitable for C-terminal coupling



*Procedure for preparation of 1-bromo-5-methylhex-2-ene:

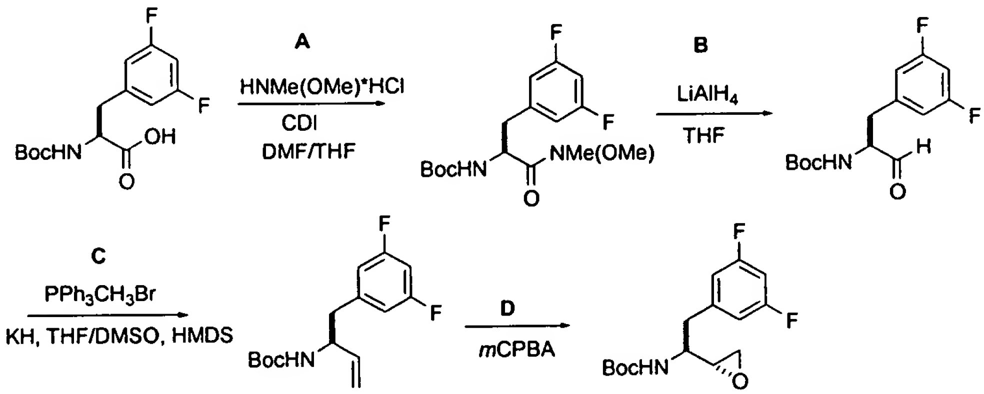


Alternatively hydroxyethylenes may be prepared by the method described below. Synthesis of the Boc-3,5-difluorophenylalanine *threo* epoxide starting material was adapted from the procedure of Luly, JR, et al. *J. Org. Chem.* **1987**, *52*, 1487-1492 for the synthesis of Boc-phenylalanine *threo* epoxide (Scheme II). The starting material utilized

in the preparation of Boc-3,5-difluorophenylalanine *threo* epoxide was Boc protected *l*-3,5-difluorophenylalanine available from Synthetech, Inc. (1290 Industrial Way, P. O. Box 646, Albany, OR 97321 USA).

Scheme II

Formation of a representative chiral epoxide precursor



The chiral amine synthesis, the initial alkylation step and further manipulation to the lactone were accomplished based on literature procedures as follows: Dragovich, PS, et al. *J. Med. Chem.* **1999**, 42, 1203-1222 ; Askin, D., et al. *J. Org. Chem.* **1992**, 57, 2771-2773. Cleavage of the Boc protecting group and subsequent coupling of the acid was accomplished using the procedures for deprotection of the amine and EDC coupling given below. Ring-opening of the lactone to the final product was accomplished using a $AlMe_3$-mediated coupling step according to the literature procedure of S.F. Martin et al., *Tetrahedron Lett.* **1998**, 39,1517-1520.

Removal of a Boc-protecting group from a protected amine to generate free amine:

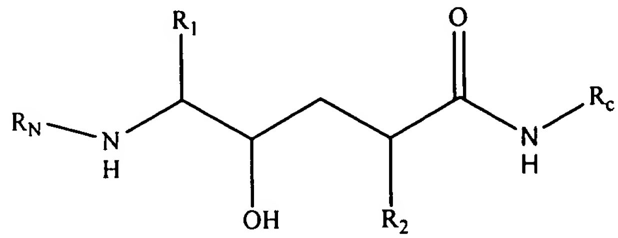
For example, the Boc-protected alpha-amino lactone intermediate of either Scheme I or II was dissolved in a trifluoroacetic acid/dichloromethane (1/1) solution. The reaction was monitored by TLC to confirm the consumption of starting material at which time the solvents were removed under reduced pressure to yield the free amine, which was used without further purification.

Coupling deprotected amine with a selected N-terminal capping group:

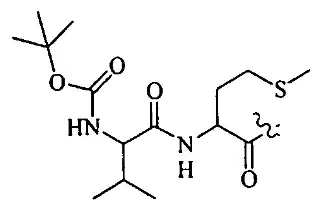
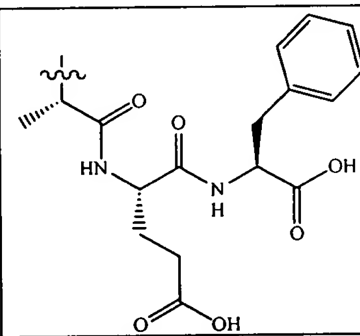
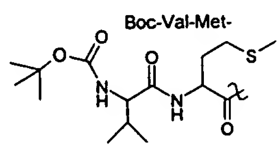
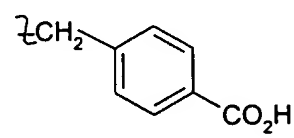
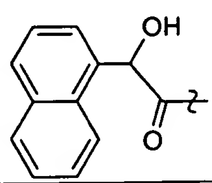
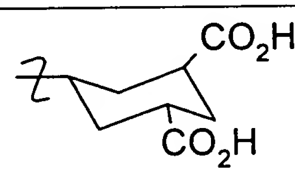
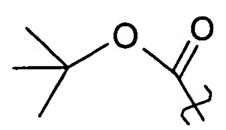
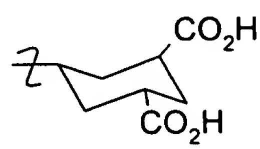
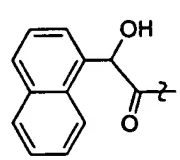
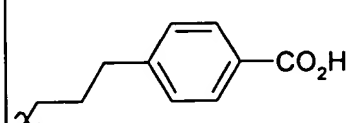
For example, 2-(N,N-dipropyl) amidobenzoic acid (1.0 equiv.) was dissolved in 30 mL of dry dichloromethane, then HOBT (2.0 equiv.), functionalized α-amino lactone from the step above (1.0 equiv.) and TEA (5 equiv.) were added and all was stirred for 20 minutes. EDC (1.2 equiv.) was added and the mixture was stirred overnight under an atmosphere of nitrogen. The reaction was then diluted with water and extracted with EtOAc (3x). The organic layers were washed with aqueous citric acid (2x), sat. NaHCO3 (2x), brine, then dried over $MgSO_4$, and the solvent was removed under vacuum. The product of this step may then be subjected to a lactone ring aminolysis to provide the desired amide bond.

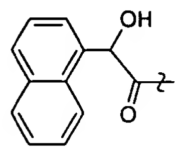
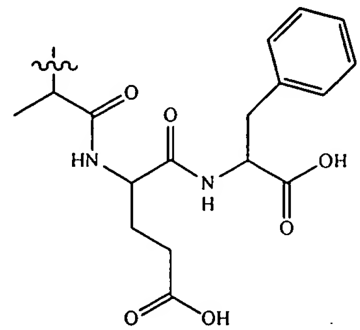
Table 1

Enzyme inhibition assay results for structures having the peptide backbone:



(XII)

Example	R_N	R_C
Examples 1-6: R2 = $-CH(CH_3)_2$ and R1 = $-CH_2CH(CH_3)_2$		
1		
2		
3		
4		
5		

6			

*Assay procedure described in the Example 70

Table 1 (con't.)

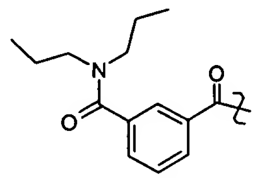
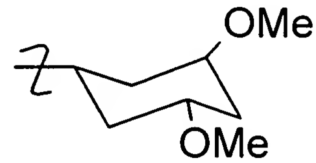
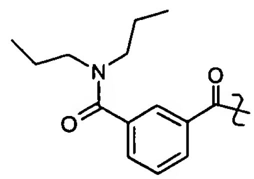
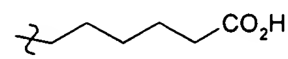
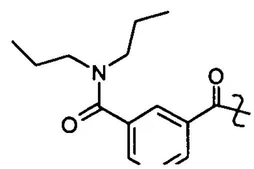
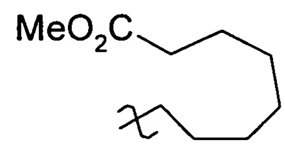
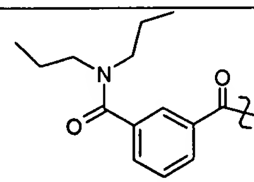
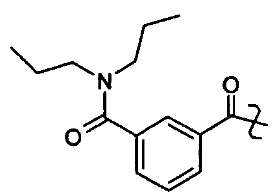
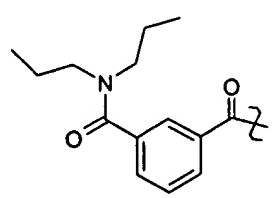
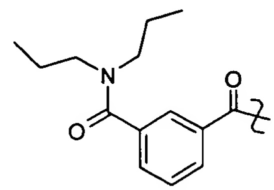
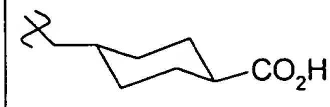
Examples 7-10: R2 = $-CH_2CH_3$ and R1 = $-CH_2$-3,5-difluorophenyl			
7			
8			
9			
10			
Example 11: R2 = benzyl and R1 = $-CH_2$-3,5-difluorophenyl			
11			
Examples 12: R2 = propyl and R1 = $-CH_2$-3,5-difluorophenyl			
12			

Table 1 (con't.)

Examples 13: R1 = methyl and R2 = $-CH_2$-3,5-difluorophenyl			
13			

Example 1

This compound was prepared employing the amino and hydroxy protected hydroxyethylene prepared via Scheme I. The compound was prepared standard resin supported peptide synthetic methods using standard HOBt, EDC coupling procedures described under Scheme II. Boc-Phe was esterified to the resin support. The Boc protecting group was removed from the Phe by treatment with trifluoroacetic acid in dicloromethane (TFA/DCM) and then coupled with Boc-Glu (mono ester) as described above. The cycle of amino deprotection and HOBt/EDC coupling was repeated with Boc-Ala, then with the protected hydroxyethylene moiety of Scheme I and then Boc-Met and finally Ac-Val. The glutamyl ester was removed via LiOH hydrolysis. The silyl group was removed from the hydroxyl function by treatment with tetra-*t*-butylammonium fluoride [(*t*-Bu)$_4$NF] in THF.

Molecular Formula	$C_{41}H_{68}N_6O_9S$
Molecular Weight	821.10
Mass spec (MH+)	821

Example 2

p-Aminomethylbenzoic acid methyl ester (commercially available) was coupled with the hydroxyethylene moiety of Scheme I using standard EDC/HOBt coupling. The Boc protecting group was removed from the N-terminal and then subsequently coupled with Boc-Val-Met. The methyl ester was hydroylzed as described above and silyl group was removed from the hydroxyl function by treatment with tetra-*t*-butylammonium fluoride [(*t*-Bu)$_4$NF] in THF.

Molecular Formula	$C_{35}H_{58}N_4O_8S$
Molecular Weight	694.927
tlc Rf (solvent)	Rf = 0.28 in 5% Methanol/dichloromethane
Purification:	5% Methanol/ dichloromethane
Mass spec (MH+)	695

Example 3

The hydroxyethylene moiety of Scheme I was coupled with the dimethyl ester of 3,5-dicarboxycyclohexylamine as prepared in Scheme VI A. This intermediate was in turn deprotected at the N-terminal with TFA/DCM and then coupled with the alpha-hydroxy-naphthylacetic acid. The methyl esters were hydrolyzed with LiOH and then the silyl group was removed from the hydroxyl function by treatment with tetra-*t*-butylammonium fluoride [(*t*-Bu)$_4$NF] in THF.

Molecular Weight	584.7
tlc Rf (solvent)	0.15 (10% MeOH/CH2Cl2)
Purification:	Flash chromatography
Mass spec (M+H+)	(CI) 584.7

Example 4

The protected hydroxyethylene as produced in Scheme I was coupled with the the dimethyl ester of 3,5-dicarboxycyclohexylamine (Scheme VI A). The diester was hydrolyzed with LiOH and the silyl protecting group removed by treatment with tetra-*t*-butylammonium fluoride [(*t*-Bu)$_4$NF] in THF.

Molecular Formula	$C_{25}H_{44}N_2O_8$
Molecular Weight	500.6
tlc Rf (solvent)	0.15 (5% MeOH/CH_2Cl_2)
Purification:	Acid/base extraction
Mass spec (M-H+)	(CI) 498.7

Example 5 (diastereomeric at the α-hydroxy-naphthylacetyl)

The hydroxyethylene moiety of Scheme I was coupled with the methyl 3-(1-aminopropyl)-4-benzoate (commercially available). This intermediate was in turn deprotected at the N-terminus with TFA/DCM (1:1) and then coupled with the alpha-hydroxy-naphthylacetic acid. The methyl ester was hydrolyzed with LiOH and then the silyl group was removed from the hydroxyl function by treatment with tetra-*t*-butylammonium fluoride [(*t*-Bu)$_4$NF] in THF.

Molecular Formula	$C_{34}H_{44}N_2O_6$
Molecular Weight	576.73
tlc Rf (solvent)	Rf = 0.12 in 10% Methanol/ dichloromethane
Purification:	10% Methanol/ dichloromethane
Mass spec (MH+)	577

Example 6

This pentapeptide isostere was prepared to test the efficacy of the α-hydroxy-naphthylacetic acid as an N-terminal group peptidomimetic in an oligopeptide sequence that demonstrated good activity (see Ex. 1). The hydroxyethylene moiety was prepared via the method of Scheme I. Resin supported synthesis was employed to prepare the molecule by bonding Boc-Phg to a resin support and then sequentially constructed by removal of the Boc protecting group and HOBt/EDC coupling in turn with glutamic acid methyl ester, valine, the hydroxyethylene isostere of Scheme I and finally with α-hydroxy-naphthylacetic acid. The product was then cleaved from the solid support and protecting groups were removed as described in the examples above.

Molecular Formula	$C_{41}H_{54}N_4O_{10}$
Molecular Weight	762.9
Purification:	500analytical HPLC trace (Gradient: 20-50% [B] in 30 minutes, [A] Buffer = 0.1%TFA/H2O; [B] Buffer =0.1%TFA/Acetonitrile) revealed two diastereomers eluting at 19.4 and 21.0 minutes
Mass spec (M+Na+) [M+K+]	763.6 (785.6) [801.6]

The preparation of examples 1-6, as described in Table 1 above, is outlined in Scheme I.

Example 7

After the C-terminal coupling was accomplished as described above, the lactone was subjected to aminolysis at refluxing temperatures with 3,5-dimethylcyclohexylamine in the presence of $AlMe_3$ and a suitable organic solvent to provide the subject compound.

Molecular Formula	C36 H51 F2 N3 O6
Molecular Weight	659
tlc Rf (solvent)	0.15 (5% iPrOH/CHCl3)
Purification:	Flash chromatography
Mass spec (M+H+)	(CI) 660.4

Example 8

After the C-terminal coupling was accomplished as described above, the lactone was subjected to aminolysis at refluxing temperatures with 6-aminohexanoic acid in the presence of $AlMe_3$ and a suitable organic solvent to provide the subject compound.

Molecular Formula	$C_{34}H_{47}F_2N_3O_6$
Molecular Weight	631
tlc Rf (solvent)	0.15 (5% MeOH/CH2Cl2)
Purification:	Flash chromatography
Mass spec (M+H+)	(CI) 632.2

Example 9

After the C-terminal coupling was accomplished as described above, the lactone was subjected to aminolysis at refluxing temperatures with 8-aminooctanoic acid in the presence of $AlMe_3$ and a suitable organic solvent which was then dissolved in MeOH and treated with HCl gas to provide the desired methyl ester.

Molecular Formula	$C_{37}H_{53}F_2N_3O_6$
Molecular Weight	673
tlc Rf (solvent)	0.4 (5% iPrOH/$CHCl_3$)
Purification:	Flash chromatography
Mass spec (M+H+)	(CI) 674.4

Example 10

After the C-terminal coupling was accomplished as described above, the lactone was subjected to aminolysis at refluxing temperatures with 4-carboxycyclohexylmethylamine in the presence of $AlMe_3$ and a suitable organic solvent to provide the subject compound.

Molecular Formula	$C_{36}H_{49}F_2N_3O6$
Molecular Weight	657
tlc Rf (solvent)	0.3 (10% MeOH/CH_2Cl_2)
Purification:	Flash chromatography
Mass spec (M+H+)	(CI) 658.4

Example 11

The subject compound was prepared as in Example 10 except that in the first step of preparation of the chiral oxazolidine intermediate, 3-phenylpropionyl chloride (Aldrich Chemical) was substituted for *n*-butanoyl chloride.

Molecular Formula	$C_{41}H_{51}F_2N_3O_6$
Molecular Weight	719.86
Mass spec (M+Na+)	743

Example 12

The subject compound was prepared as in Example 10 except that in the first step of preparation of the chiral oxazolidine intermediate, *n*-pentanoyl chloride was substituted for *n*-butanoyl chloride.

Molecular Formula	$C_{37}H_{51}F_2N_3O_6$
Molecular Weight	671.37
Mass spec (M+Na+)	694.37

Example 13

The subject compound was prepared as in Example 10 except that in the first step of preparation of the chiral oxazolidine intermediate, *n*-propionyl chloride was substituted for *n*-butanoyl chloride.

Molecular Formula	$C_{35}H_{47}F_2N_3O_6$
Molecular Weight	643.34
Mass spec (M+Na+)	666.34

The compound formulae referred to in Examples 14-22 correspond to those recited in CHART A. Furthermore, the following examples relate to those compounds recited in CHART A where R_1 = -(CH$_2$)3,5-difluorobenzyl, R_2 = Et, R_N = N',N'-dipropylisophthalamide, R_C = *anti*-4-aminomethylcyclohexanecarboxylic acid, and PROTECTING GROUP is Boc. The identity of the R_2 substituent is determined by the starting material (i.e. compounds of formula (XIII)) used in the synthesis of the intermediate (VII) as is outlined in CHART B. The intermediate (VII), prepared according to CHART B, is then incorporated into the synthetic scheme for the preparation of hydroxyethylene compounds of formula (XII), as outlined in CHART A, by reaction with the epoxide (VI).

Example 14

(L)-[2-(3,5-Difluorophenyl)-1-(methoxymethylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (III)

(L)-2-tert-Butoxycarbonylamino-3-(3,5-difluorophenyl)-propionic acid (Synthetech Inc., II, 2.66 g, 8.83 mmol) was dissolved in a mixture of dry THF (5 mL) and dry DMF (2 mL) at rt. 1,1-Carbonyldiimidazole (1.71 g, 10.6 mmol) was added in one portion to this solution. After gas evolution ceased, a solution of N-methyl-O-methylhydroxylamine hydrochloride (0.955 g, 9.79 mmol) and diisopropylethylamine (1.6 mL, 9.19 mmol) in DMF (4 mL) was added at rt by syringe. This was stirred at rt for 17 h, whereupon the reaction was quenched with 10% citric acid. The mixture was

extracted with EtOAc. The organic extract was washed (saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc/hexanes elution) to give an oil as product: M+Na+ 367.1.

Example 15

(L)-[1-(3,5-Difluorobenzyl)-2-oxoethyl]-carbamic acid tert-butyl ester (IV)

(L)-[2-(3,5-Difluorophenyl)-1-(methoxymethylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (III, 2.56 g) was dissolved in dry THF (50 mL) and cooled to 0 °C. To this mixture was added powder lithium aluminum hydride (285 mg) in portions over 5 min. The resulting suspension was stirred at 0 °C for 1 h. Reaction was quenched at 0 °C by slow addition of saturated citric acid until gas evolution ceased, followed by dropwise addition of 10% aqueous citric acid (30 mL). This was then allowed to warm to rt. The layers were separated and the aqueous extracted with Et_2O. The combined organic extracts were washed (saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a solid, which was used without further purification.

Example 16

(L)-[1-(3,5-Difluorobenzyl)allyl]-carbamic acid tert-butyl ester(V)

Potassium hydride (35% suspension in mineral oil, 1.76 g) was suspended in a mixture of dry THF (20 mL) and DMSO (4 mL), and was cooled to 0 °C. 1,1,1,3,3,3-Hexamethyldisilazane (4.0 mL) was added by syringe, and the mixture was stirred for 45 min at 0 °C. Methyltriphenylphosphonium bromide (5.57 g) was added, and the resulting yellow slurry was stirred at 0 °C for 1 h, whereupon the mixture was cooled to –78 °C. A solution of (L)-[1-(3,5-Difluorobenzyl)-2-oxoethyl]-carbamic acid tert-butyl ester (IV, 2.2 g) in THF (15 mL) at –78 °C was added by cannula. The resulting suspension was stirred at –78 °C for 15 min, then was allowed to warm to rt for 16 h. MeOH (2 mL) and half-saturated sodium bicarbonate solution (100 mL) were added, and the mixture was extracted with EtOAc (2 X 50 mL). The combined organic extracts were washed (water, saturated NaCl) dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The

residue was purified by flash chromatography (10-20% Et_2O/hexanes) to give a solid as product: M+Na+ 306.1.

Example 17

(1S, 2R)-[2-(3,5-Difluorophenyl)-1-oxiranylethyl]-carbamic acid tert-butyl ester (VI)

(L)-[1-(3,5-Difluorobenzyl)allyl]-carbamic acid tert-butyl ester(V, 3.3 g) was dissolved in CH_2Cl_2 (130 mL) and *m*-chloroperbenzoic acid (50-55% pure, 16.0 g) was added with stirring at rt. After 23 h, the reaction mixture was diluted with Et_2O, washed (10% Na_2SO_3, saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a solid: M+Na+ 322.1.

Example 18

(1*S*,2*S*, 4*R*)-[1-(3,5-Difluorobenzyl)-4-((3a*S*, 8a*R*)-2,2-dimethyl-8,8a-dihydro-3a*H*-indeno[1,2-d]oxazole-3-carbonyl)-2-hydroxyhexyl]-carbamic acid tert-butyl ester (VIII)

(1S, 2S)-[2-(3,5-Difluorophenyl)-1-oxiranylethyl]-carbamic acid tert-butyl ester (VI, 113 mg) and 1-((3a*S*, 8a*R*)-2,2-Dimethyl-8,8a-dihydro-3a*H*-indeno[1,2-d]oxazol-3-yl)-butan-1-one (VII, 94 mg) were combined in dry THF (3 mL), and cooled to –78 °C. To this solution was added BuLi (2.5 M in hexanes, 0.32 mL) over 5 min., whereupon the solution was allowed to warm to 0 °C for 1.5 h. The reaction mixture was partitioned between 0.5 N HCl (4 mL) and 1:1 EtOAc/hexanes (2 X 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20-30% EtOAc/hexanes) to give an oil: MH+ 559.1.

Example 19

[2-(3,5-Difluorophenyl)-1-(S)-(4-(R)-ethyl-5-oxo-tetrahydrofuran-2-(S)-yl)-ethyl]-carbamic acid tert-butyl ester (IX)

(1*S*,2*S*, 4*R*)-[1-(3,5-Difluorobenzyl)-4-((3a*S*, 8a*R*)-2,2-dimethyl-8,8a-dihydro-3a*H*-indeno[1,2-d]oxazole-3-carbonyl)-2-hydroxyhexyl]-carbamic acid tert-butyl ester

(VIII, 60 mg) was dissolved in 5:1 toluene/CH_2Cl_2 (3 mL), and *p*-toluenesulfonic acid monohydrate (23 mg) was added. This was stirred at rt for 18 h. The mixture was then filtered, and partitioned between half-saturated $NaHCO_3$ (3 mL) and 1:1 EtOAc/hexanes (2 X 3 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue afforded desired product as a solid: MH+ 370.2.

Example 20

5*S*-[1*S*-Amino-2-(3,5-difluorophenyl)ethyl]-3*R*-ethyldihydrofuran-2-one (X)

[2-(3,5-Difluorophenyl)-1-(S)-(4-(R)-ethyl-5-oxo-tetrahydrofuran-2-(S)-yl)-ethyl]-carbamic acid tert-butyl ester (IX, 313 mg) was dissolved in CH_2Cl_2 (1 mL) at rt, whereupon CF_3COOH (1 mL) was added. This was stirred at rt for 1 h, then concentrated under reduced pressure. This was used in the next reaction without further purification.

Example 21

N-{2-(3,5-Difluorophenyl)-(1*S*, 2*S*, 4*R*)-[1-(4-ethyl-5-oxotetrahydrofuran-2-yl)]ethyl}-N',N'-dipropylisophthalamide (XI)

5*S*-[1*S*-Amino-2-(3,5-difluorophenyl)ethyl]-3*R*-ethyldihydrofuran-2-one (X, 228 mg theoretical) was combined with triethylamine (0.7 mL) in dry DMF (2 mL) at 0 °C. N,N-Dipropylisophthalamic acid (242 mg) was added and dissolved. 1-Hydroxybenzotriazole (224 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (320 mg) were added in succession. The mixture was stirred at 0 °C for 5 min., then allowed to warm to rt for 4 h. This was then diluted with 10% citric acid, and extracted 3X with EtOAc. The combined organic extracts were washed (saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (40% EtOAc/hexanes elution) to give a solid: MH+ 501.3.

Example 22

4-(*anti*)-{[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-methyl}cyclohexanecarboxylic acid (XII)

Anti-4-Aminomethylcyclohexanecarboxylic acid (57 mg) was suspended in 1,2-dichloroethane (2 mL), and cooled to 0 °C. Trimethylaluminum (2.0 M in toluene, 0.21 mL) was added, followed by a solution of N-{2-(3,5-Difluorophenyl)-(1*S*, 2*S*, 4*R*)-[1-(4-ethyl-5-oxotetrahydrofuran-2-yl)]ethyl}-N',N'-dipropylisophthalamide (XI, 30 mg) in 1,2-dichloroethane (1 mL). This was then warmed to reflux for 1.5 h, whereupon the reaction mixture was cooled to 0 °C, and the reaction quenched with 3 N HCl (2 mL). The slurry was stirred at 0 °C for 30 min, and then extracted with 3 X 5 mL 10% iPrOH/$CHCl_3$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5-10% MeOH/CH_2Cl_2 elution) to give a solid: MH+ 658.4.

The compound formulae referred to in Examples 23-24 correspond to those recited in CHART B. Furthermore, the following examples relate to those compounds recited in CHART B R_2 = Et.

Example 23

N-(1S, 2R)-(2-Hydroxyindan-1-yl)-butyramide (XV)

(1S, 2R)-cis-1-Amino-2-indanol (XIV, 1.5 g) was dissolved with triethylamine (1.5 mL) in dry THF (45 mL), and cooled to 0 °C. Butyryl chloride (XIII, 1.05 mL) was added by syringe, and the resultant solution stirred 0 °C for 20 min, whereupon the reaction mixture was partitioned between half-saturated NH_4Cl (45 mL) and EtOAc (2 X 45 mL). The combined organic layers were dried dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a solid, which was taken to the next reaction without further purification.

Example 24

1-((3a*S*, 8a*R*)-2,2-Dimethyl-8,8a-dihydro-3a*H*-indeno[1,2-d]oxazol-3-yl)-butan-1-one (VII)

N-(1S, 2R)-(2-Hydroxyindan-1-yl)-butyramide (XV, 2.2 g) and 2-methoxypropene (5 mL) were combined with CH_2Cl_2 (70 mL) at rt, and methanesulfonic acid (0.05 mL) was added. After 20 min at rt, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an oil as product: MH+ 260.1.

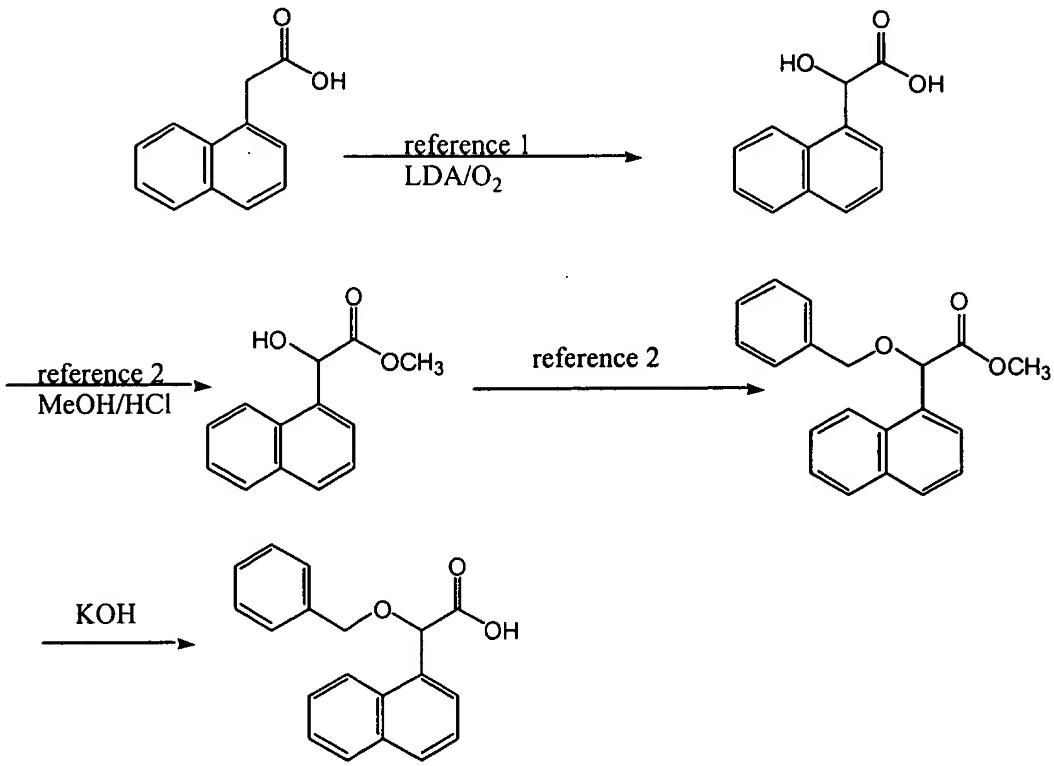
Examples 25-30 recited below relate to the synthesis for N-terminus capping groups.

Example 25

Hydroxylated and Benzylated N-terminal Capping Groups

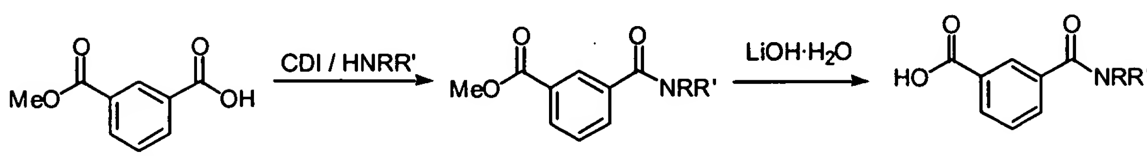
The making of hydroxylated and benzylated N-terminal capping groups from aromatic acetic acid starting materials is illustrated in Scheme III below. Moersch, GW and Zwiesler, ML. (*Synthesis*, 1971, 647-648, ref. 1 in Scheme III) demonstrate a synthesis useful for preparing an arylalkylhydroxycarboxylic acid N-terminus capping group. The procedure here provides alpha hydroxylation of 1-naphthylacetic acid, using lithium diethylamine and oxygen. Hon, Yung-Son, Chang, Rong-Chi, Chau, Tay-Yuan (*Heterocycles*, 1990, Vol. 31, No. 10, 1745-1750, ref. 2 in Scheme III) demonstrate a synthesis of the corresponding benzyl ether from the α-hydroxyaromatic by esterification of the carboxy function and etherification with benzyl bromide. Either the α-hydroxy acid or the benzyl ether derivative is suitable as a N-terminal cap.

Scheme III



Example 26
Preparation of Carboxybenzamides:

Scheme IVA



Methyl isophthalate (Aldrich Chemical, Milwaukee, WI, (1 equiv, 11.1 mmol) was dissolved in 50:50 THF : DMF (20 mL) before the addition of 1, 1' carbonyldiimidazole (CDI) (1.2 equiv, 13.3 mmol) at ambient temperature. Upon addition of CDI, an evolution of gas (CO_2), was observed. After gas evolution subsided (approximately one minute or less), the amine (1.2 equiv, 13.3 mmol) was added. After 12 h of stirring at ambient temperature, the reaction was partitioned between saturated aqueous NH_4Cl and ethyl acetate, and the aqueous layer was extracted twice more with ethyl acetate. The organic extracts were then washed with saturated aqueous solutions of $NaHCO_3$ and NaCl, and dried over anhydrous $MgSO_4$ or $NaSO_4$. Filtration of the drying

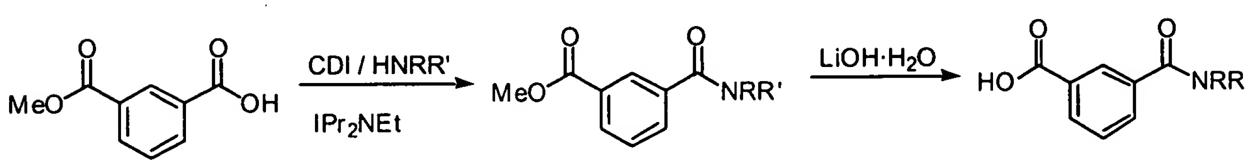
agent and removal of solvents *in vacuo* gave the crude white solid or clear oil. Purification of these compounds *if needed* was achieved via chromatography on silica gel with 30–40% ethyl acetate in hexanes.

The methyl isophthalate mono-alkyl or di-alkyl amide was then treated with $LiOH{\cdot}H_2O$ (3 equiv, 33.3 mmol) in a minimum amount of 1:2:1 THF:MeOH:H_2O and allowed to stir overnight at ambient temperature. After 12 h, the solvents were removed *in vacuo* and subsequently partitioned between H_2O and ethyl acetate. If emulsions prohibit separation of the two layers, a small amount of brine was added to aid in separation. The aqueous layer was extracted once more with ethyl acetate (to remove any unreacted starting material). The aqueous layer was then acidified with concentrated HCl until pH $\leq$ 3. The cloudy-white acidic aqueous solution thus obtained was then extracted three times with ethyl acetate. These combined organic extracts were dried over anhydrous $MgSO_4$ or $NaSO_4$. Filtration of the drying agent and removal of solvents *in vacuo* gave a solid. The mono- or di-alkyl amide isophthalate was used crude in the next reaction.

Example 27

Preparation of Carboxybenzamides

Scheme IVB



Methyl isophthalate (1 equiv, 11.1 mmol) was dissolved in 50:50 THF : DMF (20 mL) before the addition of 1, 1' carbonyldiimidazole (CDI) (1.2 equiv, 13.3 mmol) at ambient temperature. Upon addition of CDI, evolution of gas (CO_2), was observed. After gas evolution subsided (approximately one minute or less), the amine (1.2 equiv, 13.3 mmol) dissolved in DMF and diisopropylethyl amine (1.2 equiv, 13.3 mmol) was added. After 12 h of stirring at ambient temperature, the reaction was partitioned between saturated aqueous NH_4Cl and ethyl acetate, and the aqueous layer was extracted twice more with

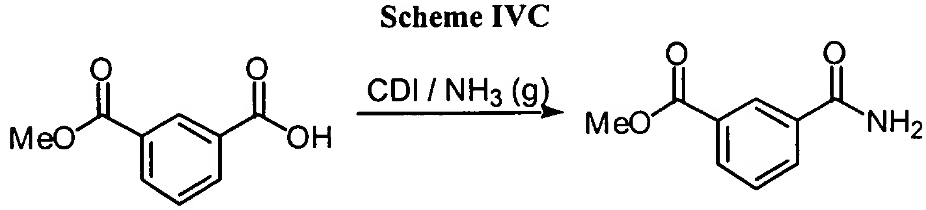
ethyl acetate. The organic extracts were then washed with saturated aqueous solutions of $NaHCO_3$ and NaCl, and dried over anhydrous $MgSO_4$ or $NaSO_4$. Filtration of the drying agent and removal of solvents *in vacuo* gave a solid or oil. Purification of these compounds *if needed* was achieved via chromatography on silica gel with 30–40% ethyl acetate in hexanes.

The methyl isophthalate mono-alkyl or di-alkyl amide (1 equiv, 11.1 mmol) was then treated with $LiOH \cdot H_2O$ (3 equiv, 33.3 mmol) in a minimum amount of 1:2:1 THF:MeOH:H_2O and allowed to stir overnight at ambient temperature. After 12 h, the solvents were removed *in vacuo* and subsequently partitioned between H_2O and ethyl acetate. If emulsions prohibit separation of the two layers, a small amount of brine was added to aid in separation. The aqueous layer was extracted once more with ethyl acetate (to remove any unreacted starting material). The aqueous layer was then acidified with concentrated HCl until pH ≤ 3. The cloudy-white acidic aqueous solution thus obtained was then extracted three times with ethyl acetate. These combined organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4. Filtration of the drying agent and removal of solvents *in vacuo* gave a solid. The mono- or di-alkyl amide isophthalate was used crude in the next reaction.

Example 28

Preparation of Primary Amide

Scheme IVC

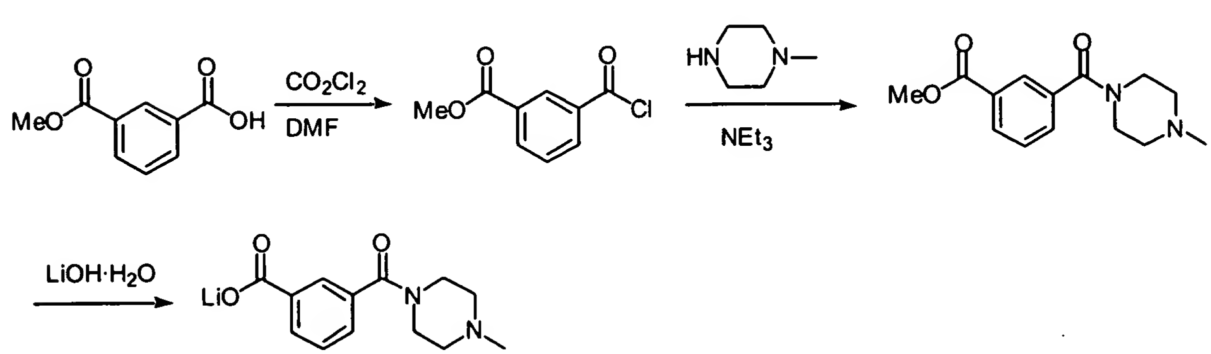


Methyl isophthalate (1 equiv, 11.1 mmol) was dissolved in 50:50 THF : DMF (20 mL) before the addition of 1, 1' carbonyldiimidazole (CDI) (1.2 equiv, 13.3 mmol) at ambient temperature. Upon addition of CDI, an evolution of gas (CO_2), was observed. After five minutes, ammonia gas was bubbled into the solution through a syringe needle for 1 h. Since the reaction was heating up due to an exotherm, the reaction was cooled to

0 °C for the duration of the hour. The reaction was then left stirring under a balloon of ammonia overnight at ambient temperature. After 12 h, the reaction was partitioned between saturated aqueous NH_4Cl and ethyl acetate, and the aqueous layer was extracted twice more with ethyl acetate. The organic extracts were then washed with saturated aqueous solutions of $NaHCO_3$ and NaCl, and dried over anhydrous $MgSO_4$ or $NaSO_4$. Filtration of the drying agent and removal of solvents *in vacuo* gave a solid or oil. Purification via chromatography on silica gel with 5% isopropanol in chloroform gave the desired primary amide.

The methyl isophthalate primary amide (7.26 mmol) was then treated with $LiOH \cdot H_2O$ (3 equiv, 21.8 mmol) in a minimum amount of 1:2:1 THF:MeOH:H_2O and allowed to stir overnight at ambient temperature. After 12 h, the solvents were removed *in vacuo* and subsequently partitioned between H_2O and ethyl acetate. The aqueous layer was extracted once more with ethyl acetate (to remove any unreacted starting material). The aqueous layer was then acidified with concentrated HCl until pH ≤ 3. The cloudy-white acidic aqueous solution thus obtained was then extracted three times with ethyl acetate. These combined organic extracts were dried over anhydrous $MgSO_4$ or $NaSO_4$. Filtration of the drying agent and removal of solvents *in vacuo* gave a solid. The mono- or di-alkyl amide isophthalate was used crude in the next reaction.

Example 29
Preparation of Heterocyclic Amides



Scheme IVD

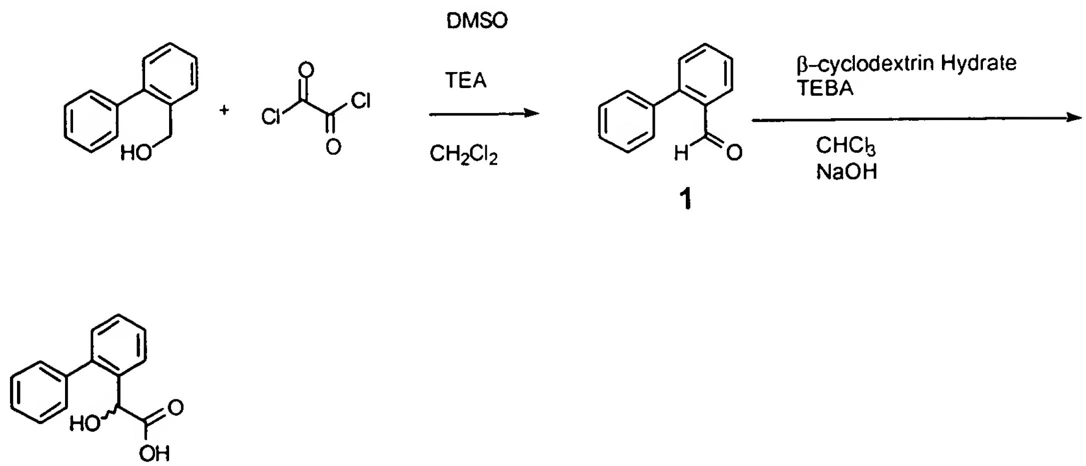
Methyl isophthalate (1.2 equiv, 2.78 mmol) was dissolved in dry CH2Cl2 and three drops of DMF (catalytic). The solution was cooled to 0 °C before the drop-wise addition of oxalyl chloride (2 equiv, 4.63 mmol). The mixture was stirred at 0 °C for 1 h. The mixture never dissolved. After 1 h, the solvents were removed *in vacuo*. The acid chloride was left under vacuum overnight.

The crude acid chloride (1 equiv, 2.78 mmol) was dissolved in dry CH_2Cl_2 and cooled to 0 °C before the addition of NEt_3 (5 equiv, 11.6 mmol) and N-methyl piperidine (6 equiv, 13.9 mmol). The reaction was stirred at 0 °C for 2 h before the solvents were removed *in vacuo*. The residue was diluted with H_2O and ethyl acetate and the layers were separated. The aqueous layer was extracted twice more with ethyl acetate, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. Filtration of the drying agent and removal of solvents *in vacuo* gave the crude product.

The crude amide (1 equiv, 2.19 mmol) was then treated with $LiOH{\cdot}H_2O$ (1 equiv, 2.19 mmol) in a minimum amount of 1:2:1 THF:MeOH:H_2O and allowed to stir overnight at ambient temperature. After 12 h, the solvents were removed *in vacuo* and subsequently partitioned between H_2O and ethyl acetate. The aqueous layer was extracted once more with ethyl acetate (to remove any unreacted starting material.) Removal of H_2O from aqueous layer *in vacuo* gave a solid.

Example 30
Preparation of aromatic α-hydroxy acids
(illustrated by the preparation with α-hydroxy-α-(2-biphenyl)acetic acid)

Scheme V



2

A solution of CH_2Cl_2 (25 mL) and oxalyl chloride (2 mL, 21.16 mmol) was placed in a 100-mL round bottom flask kept under nitrogen. The oxalyl chloride solution was stirred at –50 to –60 ^{0} C. Me_2SO (2.5 mL, 35.82 mmol) was dissolved in CH_2Cl_2 (5mL). The Me_2SO was added dropwise to the stirred oxalyl chloride solution at –50 to – 60 ^{0} C. The reaction mixture was stirred for 2 min and the 2-phenylbenzyl alcohol (16.28 mmol in 10 mL CH_2Cl_2) was added within 5 min; stirring was continued for an additional 60 min. TEA (11.30 mL, 81.4 mmol) was added and the reaction mixture was stirred for 60 min and then allowed to warm to room temperature. Water (60 mL) was then added and the aqueous layer was reextracted with additional CH_2Cl_2 (60 mL). The organic layers were combined, washed with saturated NaCl solution (120 mL), and dried over anhydrous $MgSO_4$. The filtered solution was concentrated in a rotary evaporator to dryness. The oil was chromatographed on silica gel (98: 2 hexanes: EtOAc) to give **1**.

A mixture of 5.46 mmol of aromatic aldehyde(1) in 10 mL of $CHCl_3$ and β-cyclodextrins (CDs) (0.11 mmol) and triethylbenzylammonium chloride(TEBA)(0.273 mmol)in a flask equipped with a magnetic stirrer and dropping funnel was stirred for 20 minute at 50 ^{0} C. Then 10 g of sodium hydroxide dissolved in 10 mL of water was added dropwise to the flask with stirring. After completion of this addition, the reaction was

continued for 8 h with the temperature maintained at 50 ^{0} C. Then enough of distilled water was added to dissolve the precipitate formed during the reaction, and the resulting solution was thoroughly washed with ether, adjusted to pH 3 with dilute hydrochloric acid and extracted with 3 x 30 mL of ether. The extract was dried with anhydrous sodium sulfate, then evaporated to dryness and the remaining precipitate was subjected to column chromatography on silica gel using DCM: MeOH :AcOH (95: 5: 1) to give **2.**

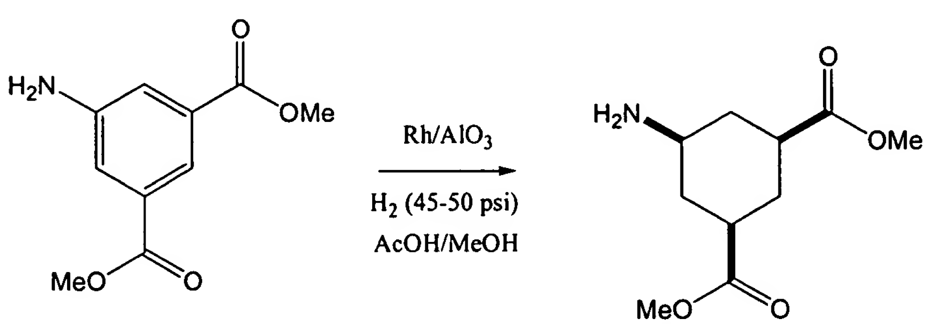
Examples 31 and 32 recited below relate to the synthesis for N-terminus capping groups.

Example 31

1-Amino-3, 5-cis,cis-dimethyl Cyclohexyldicarboxylate

To 10 g (47.85mmole) of dimethyl-5-isophthalate in 25 ml of acetic acid and 50 ml of methanol was added 5 g of 5% rhodium in alumina in a high-pressure bottle, which was saturated with hydrogen at 55 psi and shaken for one week of time.

Scheme VI A



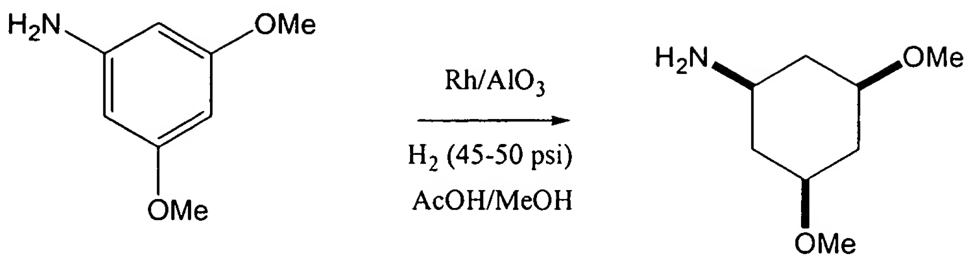
The mixture was then filtered through a thick layer of Celite cake and rinse with methanol three times, the solvents was concentrated and the crude solid was triturated with diethyl ether and filtered again, it afforded 1-amino-3, 5-cis,cis-dimethyl cyclohexyldicarboxylate, reverse phase HPLC has shown a purity of 94.4%.

Example 32

1-Amino-3, 5-cis,cis-dimethoxy Cyclohexane

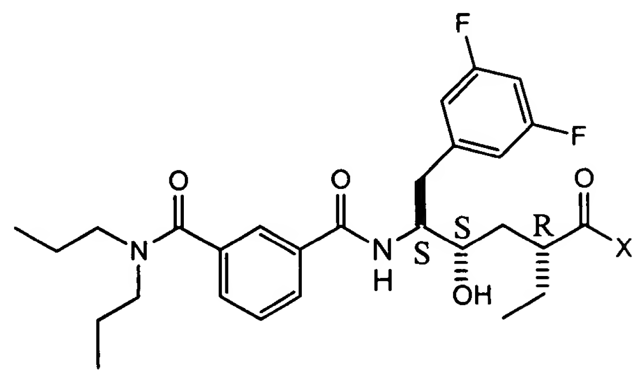
To 10 g (65.36mmole) of 3,5-dimethoxyaniline was reacted as described in the procedure above and afforded 1-amino-3, 5- cis,cis-dimethoxy cyclohexane.

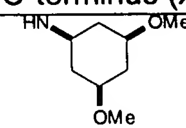
Scheme VI B

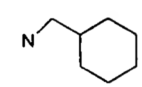
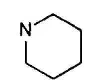
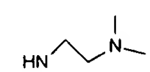


Following the general procedure as outlined in Examples 14-22 and making non-critical variations the following substitute amines of formula (XII) are obtained. These substitute amines of formula (XII) are listed in Tables 2, 3, and 4 as Examples.

Table 2



	Example	MH+	C-terminus (X)
N-[(1*S*, 2*S*, 4*R*)-1-(3,5-Difluorobenzyl)-4-(*syn*, *syn*)-(3,5-dimethoxycyclohexylcarbamoyl)-2-hydroxyhexyl]-*N,N*-dipropylisophathalamide	33	660.4	
6-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-hexanoic acid	34	632	$NH(CH_2)_5CO_2H$
5-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-pentanoic acid	35	618.3	$NH(CH_2)_4CO_2H$
4-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-butyric acid	36	603.7	$NH(CH_2)_3CO_2H$

	Example	MH+	C-terminus (X)
3-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-propionic acid	37	590.3	$NH(CH_2)_2CO_2H$
8-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-octanoic acid	38	660.4	$NH(CH_2)_7CO_2H$
8-[6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-octanoic acid methyl ester	39	674.4	$NH(CH_2)_7CO_2Me$
N-[4-(*R*)-Butylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	40	574.3	NHBu
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(R)-isobutylcarbamoyl-hexyl]-*N,N*-dipropyl-isophthalamide	41	574.5	NHiBu
N-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	42	608.3	NHBn
N-[4-(*R*)-(Cyclohexylmethyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	43	614.3	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(piperidine-1-carbonyl)-hexyl]-*N,N*-dipropyl-isophthalamide	44	586.3	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(2-dimethylamino-ethylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	45	589.3	

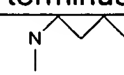
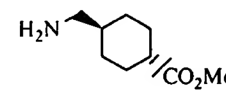
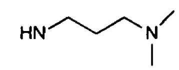
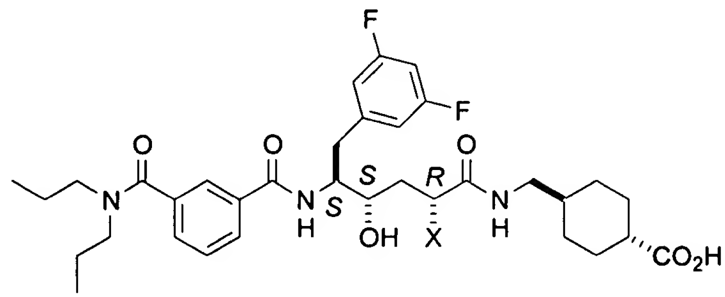
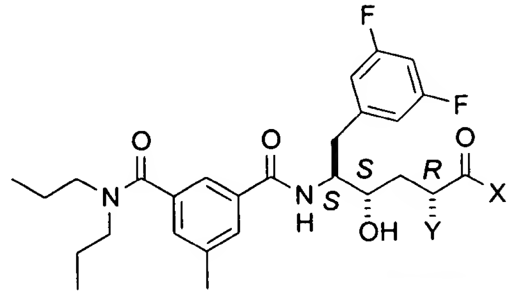
	Example	MH+	C-terminus (X)
N-[4-(*R*)-(Butyl-methyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	46	588.1	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(3-hydroxy-propylcarbamoyl)-hexyl]-*N,N*-dipropyl-isophthalamide	47	576.3	
4-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester	48	672.0	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(3-dimethylamino-propylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide	49	608.0	

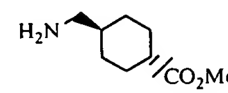
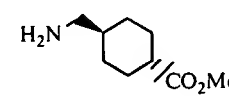
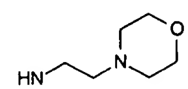
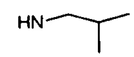
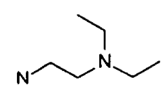
Table 3



	Example	MH+	X
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	50	658.4	Et
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-methyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	51	644.3	Me
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-propyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	52	672.3	nPr
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxyl-2-(*R*)-isobutyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	53	686.3	iBu
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	54	630.3	H
4-(*anti*)-([2-(*R*)-Benzyl-6-(3,5-difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	55	720.3	Bn

Table 4



	Example	MH+	X	Y
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(S)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid	56	672.2		Et
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(S)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester	57	686		Et
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(2-morpholin-4-yl-ethylcarbamoyl)-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	58	631.2		Me
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-isobutylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	59	574.3		Me
N-[4-(*R*)-(2-Diethylamino-ethylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	60	617.3		Me

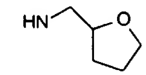
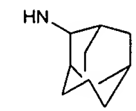
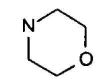
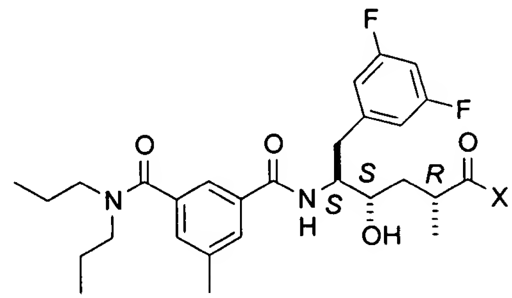
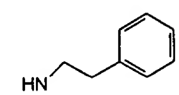
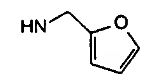
	Example	MH+	X	Y
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-pentyl)-5-methyl-*N,N*-dipropyl-isophthalamide	61	602.3		Me
N-[4-(*R*)-(Adamantan-2-ylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	62	652.3		Me
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-methyl-5-morpholin-4-yl-5-oxo-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	63	588.3		Me
N-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	64	608.3	NHBn	Me
N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(4-fluoro-benzylcarbamoyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	65	626.3	NH-(4-F)-Bn	Me

Table 5



Compound	Example	MH+	X
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-phenethylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide	66	622.3	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-[(furan-2-ylmethyl)-carbamoyl]-2-(S)-hydroxy-pentyl)-5-methyl-*N,N*-dipropyl-isophthalamide	67	598.3	
N-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(prop-2-ynylcarbamoyl)-pentyl]-5-methy-*N,N*-dipropyl-isophthalamide	68	556.3	

Example 69

Benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2R)-oxiranyl]ethylcarbamate (VI)

Following the general procedure of EXAMPLE 17 and making non critical variations but starting with the alcohol (IV) Benzyl (1S, 2R)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate, the title compound is obtained.

Example 70

Enzyme Inhibition Assay

The compounds of the invention were analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of β-secretase cleavage of a model APP substrate, MPB-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. Human brain β-Secretase was prepared from partially purified concentrated human brain tissue as described in Sindha et.al., 1999, Nature 402:537-554 and maintained in 0.20% Triton. Alternatively, recombinant full length enzyme (amino acids 1-501) was prepared from 293 cells expressing the transgenic enzyme.

Inhibition data was obtained from an ELISA which uses an anti-MBP capture antibody deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with the anti-SW192 specific biotinylated reporter antibody, and incubation with streptavidin/alkaline phosphatase. Cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, with the new SW-192 antibody-positive epitope exposed at the carboxy terminus. Detection was effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detected cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

Compounds were diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) which took up one 96-plate row per compound tested.

Procedure:

Each of the test compounds was weighed out into a vial and DMSO was added to make up a 10mM solution. To obtain a final compound concentration of 200 μM at the high point of a 6-point dilution curve, 100 μL of the 10 mM solution was added to well C1 of a 96-well V-bottom plate. Fifty μL of DMSO was added to odd wells of row C across the plate and 1:1 serial dilutions were made. 10 μL of each dilution was added to each of two wells on row C of a corresponding V-bottom plate to which 190 μL of 52 mM NaOAc/7.9% DMSO, pH 4.5 were pre-added. The NaOAc diluted compound plate was spun down to pellet precipitant and 20 μL/well was transferred to a corresponding flat-bottom plate to which 30 μL of ice-cold enzyme-substrate mixture (2.5 μL MBP-C125SW substrate, 0.03 μL enzyme and 24.5 ice cold 0.09% TX100 per 30 μl) was added. The compound concentration in the final enzyme reaction was thus 50 times less than the starting concentration. The final reaction mixture of 200 μM compound for the highest curve point was in 5% DMSO, 20 mM NaAc, 0.06% TX100, at pH 4.5. The enzyme reaction was started by warming the plates to 37° C. After 90 minutes at 37° C, 200 μL/well cold specimen diluent was added to stop the reaction and 20 μL/well was transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 μL/well specimen diluent. This reaction was incubated overnight at 4°C and the ELISA was developed the next day after a 2 hr. incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and flourescent substrate. The signal was read on a fluorescent plate reader.

Results:

Relative compound inhibition potency was determined by calculating the concentration of compound that showed a fifty- percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added compound.

For the purpose of grouping inhibitor activities of the compounds of the present invention disclosed in the data tables of this specification, the inhibitory activities have been ranked by their IC_{50} concentrations according to following order:

Group I:	compounds having an IC_{50} less than 10 μM;
Group II:	compounds having an IC_{50} of from 10 μM to and including 100 μM;
Group III:	compounds having an IC_{50} of from 100 μM to and including 200 μM;
Group IV:	compounds having an IC_{50} of greater than 200 μM.

Example 71

~~Cell Free Inhibition Assay utilizing APP-KK~~

The synthetic APP substrate, Biotin-KVEANYEVEGERC(oregon green)KK, having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue was used. The N-terminal biotin is used to anchor the peptide to a substrate assay plate. Incubation was conducted under the following conditions: 10μM APP substrate; 50nM enzyme (hAsp2a), pH 4.5, 37^{O}C, for 2 hours. Activity of the β-secretase enzyme is detected as the loss of oregon green flurophore, on the opposite side of the cleavage site from the Biotin anchor is released on cleavage of the substrate.

Incubation in the presence or absence of compound inhibitor demonstrates ~~specific inhibition of β-secretase enzymatic cleavage of its APP substrate.~~

Example 72

β-secretase inhibition: P26-P4'SW assay

~~The P26-P4'sw substrate is a peptide of the sequence:~~ (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF (SEQ ID NO:1).

The P26-P1 standard has the sequence: ~~(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL (SEQ ID NO:2).~~

Peptides were prepared by Anaspec, Inc. (San Jose, CA) using solid phase synthesis with boc-amino acids. Biotin was coupled to the terminal cysteine sulfhydryl by Anaspec, Inc. after synthesis of the peptide, using EZ-link Iodoacetyl-LC-Biotin

(Pierce). Peptides are stored as 0.8-1.0 mM stocks in 5 mM Tris, with the pH adjusted to around neutral (pH 6.5-7.5) with sodium hydroxide.

For the enzyme assay, the substrate concentration can vary from 0 - 200 μM. Specifically for testing compounds for inhibitory activity, substrate concentration can be 1.0 μM. Compounds to be tested are added in DMSO, with a final DMSO concentration of 5%; in such experiments, the controls also receive 5% DMSO. Concentration of enzyme is varied, to give product concentrations with the linear range of the ELISA assay (125 - 2000 pM, after dilution).

These components are incubated in 20 mM sodium acetate, pH 4.5, 0.06% Triton X-100, at 37 degrees C for 1 to 3 hours. Samples are diluted 5-fold in specimen diluent (for example, 145.4 mM sodium chloride, 9.51 mM sodium phosphate, 7.7 mM sodium azide, 0.05% Triton X-405, 6 gm/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for the ELISA as needed.

For the ELISA, Costar High Binding 96-well assay plates (Corning, Inc., Corning, NY) are coated with SW 192 monoclonal antibody from clone 16A7, or a clone of similar affinity. P26-P1 standards are diluted in specimen diluent to a final concentration of 0 to 2 nM. Diluted samples and standards (100 μl) are incubated on the SW192 plates at 4 degrees C for 24 hours. The plates are washed 4 times in TTBS buffer (150 mM sodium chloride, 25 mM Tris, 0.05% Tween 20, pH 7.5), then incubated with 0.1 ml/well of streptavidin - alkaline phosphate (Roche Molecular Biochemicals, Indianapolis, IN) diluted 1:3000 in specimen diluent. After incubating for one hour at room temperature, the plate is washed 4 times in TTBS, and incubated with fluorescent substrate solution A (31.2 gm/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, adjusted to pH 9.5 with HCl). Fluorescent values are read after 30 minutes.

Compounds that are effective inhibitors of β-secretase activity demonstrate reduced cleavage as compared to a control.

Example 36

Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared which incorporate the known cleavage site of β-secretase, and optionally detectable tags, such as fluorescent or chromogenic

moieties. Examples of such peptides, as well as their production and detection methods are described in allowed U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

~~By way of example, one such peptide has the sequence SEVNL DAEF (SEQ ID~~ NO: 3), and the cleavage site is between residues ~~5 and 6.~~ Another preferred substrate has the sequence AD~~RGLTTRP~~GSGLTNIKTEEISEVNLDAE F (SEQ ID NO: 4), and ~~the cleavage site is between residues 26 and 27.~~

These synthetic APP substrates are incubated in the presence of β-secretase under conditions sufficient to result in β-secretase mediated cleavage of the substrate. Comparison of cleavage results in the presence of the compound inhibitor results to a control provides a measure of the compound's inhibitory activity.

Example 73

Inhibition of β-secretase activity - cellular assay

An exemplary assay for the analysis of inhibition of β-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) stably transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce Aβ (Citron et.al., 1992, Nature 360:672-674). The cells were plated in 96 well plates and in Dulbecco's Modified Eagle's medium (DMEM, Sigma D-6546) containing 10% fetal bovine serum. After cells are established (1 day post plating), cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally from 0.25 to 5.0 μg/ml, and with a final concentration of DMSO ranging from 0.1 to 0.5%. After incubation at 37° C for two hours, the media is aspirated from the cells and is replaced with fresh compound for an additional 2 hour incubation. At the end of the treatment period, each cell plate is centrifuged at 1100 rpm for 5 minutes at room temperature.

Conditioned media is analyzed for β-secretase activity by analysis of release of the peptide fragment Aβ into the culture medium by immunoassay. Using specific antibodies to detect cleavage product, for example, Aβ, the enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of β-secretase mediated cleavage of APP substrate.

Example 74

Inhibition of β-secretase Activity in Primary Neuronal Cells and Human Fetal Brain Tissue

Inhibition of β-secretase activity in primary neuronal cells in mice and fetal brain tissue in humans is assayed as follows.

Media preparation

Mouse neuronal media without KCl is supplemented with the following: 25 ml fetal bovine serum (FBS, Sigma F-2422 or JRH Biosciences, 12103-78P), heat inactivated for 1 hour at 56°C; and 25 ml Chang's supplement (Irvine Scientific C104). Final concentrations in 500 ml of mouse neuronal media without KCl is 5% FBS, 5% Chang's supplement.

Human neuronal media without KCl is supplemented with the following: 10 ml of 50x stock B27 solution (Gibco 17504-036). Final concentration in 500 ml human neuronal media without KCl is 1x B27.

Preparation of cell culture plates

Polyethyleneimine (PEI) solution (50% w/v, obtained from Sigma, P-3143) is diluted 1:10 with tissue culture grade water to yield 5% (w/v) diluted solution. The PEI diluted solution is then filter sterilized, using a 0.45μm filter. Filter sterilized PEI is further diluted 1:100 with sodium borate buffer (150 mM, pH 8.5, sterile) to yield 0.05% (w/v) working solution.

Cell culture plates (24-well flat-bottom, Corning 25820, or 6-well flat-bottom, Corning 25810) are prepared for culture as follows. PEI working solution is added in an amount of 300 μl/well in 24-well plates, or 1.5 ml/well in 6 well plates to coat at approximately 80 $\mu g/cm^2$. The coated plates are incubated overnight at room

temperature. Next, the plates are aspirated and washed twice with 500 μl/well (for 24-well plates) or 2.5 ml/well (for 6-well plates) PBS (1X phosphate-buffered saline, pH 7.5, sterile). The plates are then aspirated and incubated with neuronal media without KCl plus 10% PBS (500 μl/well, 24 well; or 2.5 ml/well, 6-well) at 37°C for at least one hour. After incubation, the plates can be used immediately, or stored under sterile conditions at 37°C for up to one week (media should be discarded prior to seeding).

Preparation of PDAPP mouse cortical cultures

Wild type, Swiss Webster female mice are mated with homozygotic PDAPP male mice. Sixteen to seventeen days post mating, pregnant females are euthanized by carbon dioxide suffocation. Under sterile conditions, fetuses are removed and decapitated. Fetal brains are removed, and the cerebral cortices are dissected away from the rest of the brain tissue using a dissecting microscope. Cortical tissues are transferred to a 35 mm tissue culture dish (Corning 25000) containing ice cold Hanks buffered salt solution (HBSS, Sigma H9269).

Cortical tissues from ten mouse brains are pooled by transferring to a 50 ml polypropylene conical tube (Falcon 2070), and washed twice with 25 ml cold HBSS. Tissues are resuspended in 5 ml cold CMF HBSS (Calcium- and magnesium-free HBSS, Sigma H-9394) plus 0.5 ml DNase stock solution (Sigma D-4527, 1 mg/ml in CMF HBSS) to yield approximately 100 μg/ml final concentration of DNase. Tissue is triturated with a 5 ml pipette until the suspension becomes homogeneous (approximately 20-30 times). The cell suspension is centrifuged in a clinical centrifuge for three minutes at approximately 600 x g. The cell pellet is resuspended in 2.5 ml trypsin-EDTA (1X trypsin-EDTA, Sigma T-3924), and incubated at 37°C for five minutes.

Neuronal media plus 10% FBS (Sigma F-2422 or JRH Biosciences 12103-78P) is added in an amount of 10 ml to 1 ml DNase stock solution. The solution is mixed gently and incubated at room temperature for three minutes. The cell suspension is filterd by passage through a sterile nylon screen (100 μm pore size, Falcon 2360). The filtrate is centrifuged in a clinical centrifuge for three minutes at approximately 600 x g.

The cell pellet is recovered and resuspended in 5 ml complete mouse media, prepared as described above. Cells are counted with a hemacytometer by mixing 50 μl cell suspension with 450 μl trypan blue solution (0.4%, Sigma T-8154). Cells are diluted

to 1.2 x 10^6 cells/ml with mouse media. Cells are then plated 0.5 ml/well in 24-well plates coated with PEI, prepared as described above. Cultures are fed twice per week by complete exchange of media.

Preparation of human fetal cortical cultures

Human fetal brain tissue is obtained from Advanced Bioscience Resources (Alameda, CA). Fetal brain tissue is used promptly upon harvesting, and work is performed in a class II hood. Tissue is processed by identifying the cerebral cortex, and removing all traces of meninges with sterile forceps.

Cortical tissues are pooled by transferring to a 50 ml conical tube. Pooled cortical tissues are then washed twice with 25 ml cold HBSS. Tissues are then rsuspended in 10 ml cold CMF HBSS (Sigma H-9394) plus 1 ml DNase stock solution (Sigma D-4527) to yield approximately 100 μg/ml final concentration of DNase. Tissue is triturated with a 10 ml pipette until the suspension becomes homogeneous (approximately 20-30 times). The cell suspension is centrifuged in a clinical centrifuge for three minutes at approximately 600 x g. The cell pellet is resuspended in 10 ml trypsin-EDTA (1X trypsin EDTA, Sigman T-3924), and incubated at 37°C for five minutes. Neuronal media plus 10% FBS is added in an amount of 10 ml to 1 ml DNase stock solution. The solution is mixed gently and incubated at room temperature for three minutes.

The cell suspension is then filtered by passage through a sterile, nylon screen (as described above). The filtrate is then centrifuged as above. The cell pellet is resuspended in 5 ml human media (prepared as described above). Cells are counted with a hemacytometer by mixing 50 μl cell suspension with 450 μl trypan blue solution. Cells are diluted to 1.2 x 10^6 cells/ml with complete media (prepared as described above). The cell suspension is then plated 2 ml/well in 6-well plates coated with PEI, prepared as described above.

The cells are not disturbed for the first week. After that time, cultures are fed twice per week by complete exchange of media.

Neuronal culture Aβ assays

Mature cultures are incubated with 300 μl/well (mouse) or 750 μl/well (human) fresh media for 24 hours to generate baseline Aβ values. Conditioned media are collected and stored at -20°C until assayed.

Cultures are then treated with 300 μl/well (mouse) or 750μl/well (human) fresh media containing compound at the desired range of concentrations for 24 hours. Conditioned media are collected and stored at -20°C until assayed.

For total Aβ measurements and $A\beta_{1-42}$ measurements, 100 μl/well is analyzed by ELISA. Inhibition of production for both total Aβ and $A\beta_{1-42}$ are determined by the difference between the Aβ values for the compound treatment and baseline periods. Dose response curves are plotted as percent inhibition versus compound concentration.

At the end of this treatment period, cell viability is tested by MTT cytotoxicity assay. After conditioned media is removed from cell plates for Aβ measurement by ELIA, 25 μl of MTT stock (Sigma M-5655 at 5 mg/ml in 1x PBS, aliquoted and stored at -20°C) are added to all wells. Cell plates are incubated at 37°C in a CO_2 incubator for 1 hour. MTT lysis buffer is added in an amount of 125 μl to each well, and plates are placed on a titer plate shaker at low setting overnight. Plates are read in a microplate reader at 562-650 nm. Cell viability is calculated by percent of control cell optical density (OD).

Example 75

Inhibition of β-secretase in animal models of AD

Various animal models can be used to screen for inhibition of β-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, and the like. The animals used can be wild type, transgenic, or knockout models. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,912,410 and 5,811,633. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein.

Aniamls are administered an amount of the compound inhibitor formulated appropriately in PBS. Control animals are untreated, or treated with an inactive compound. Administration is repeated daily for a period of days. Beginning on day 0, brain tissue or fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including Aβ, using the specific antibodies to Aβ. At the end of the test period, animals are sacrificed and brain tissue or fluid is analyzed for the presence of Aβ and/or beta amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors are expected to demonstrate reduced Aβ in brain tissues and fluids, and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

Example 76

Inhibition of Aβ production in human patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of Aβ in the brain. AD patients are administered an amount of the compound inhibitor diluted in PBS. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognative and memory tests are performed once per week.

Patients administered the compound inhibitors are expected to demonstrate cognative and memory scores are expected to slow and/or stabilize as compared with non-treated patients.

Example 77

Prevention of Aβ production in patients at risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Muation, and/or by monitoring diagnostic parameters. Patieints identified as predisposed or at risk for developing AD patients are administered an amount of the compound inhibitor diluted in PBS. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognative and memory tests are performed once per month.

Patients administered the compound inhibitors are expected to demonstrate cognative and memory scores are expected to remain stable as compared with non-treated patients.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereby and should only be construed by interpretation of the scope of the appended claims.